Acid-Base Disorders

Clinical Evaluation and Management

Alluru S. Reddi

Springer

SHOUT
SHARE
IT

Acid-Base Disorders

Alluru S. Reddi

Acid-Base Disorders

Clinical Evaluation and Management

Springer

Alluru S. Reddi
Professor of Medicine, Department of Medicine, Chief, Division of Nephrology and Hypertension
Rutgers New Jersey Medical School
Newark, NJ, USA

ISBN 978-3-030-28894-5 ISBN 978-3-030-28895-2 (eBook)
https://doi.org/10.1007/978-3-030-28895-2

© Springer Nature Switzerland AG 2020
This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Acid-base physiology is a difficult topic in medicine because of its complexity. The purpose of writing this book is to present a clear and concise understanding of the fundamentals of acid-base physiology and its associated disorders that are frequently encountered in clinical practice. Each clinical acid-base disorder begins with pathophysiology followed by case studies and questions with explanations. I believe that this kind of approach will increase the knowledge of a physician in managing acid-base disturbances.

This book would not have been possible without the help of many students, house staff, and colleagues who made me understand acid-base disorders and manage patients appropriately. I am grateful to all of them. I am extremely thankful and grateful to my family for their immense support and patience. I extend my thanks to Andy Kwan and Gregory Sutorius, Springer, New York, for their continued support, help, and advice. Constructive critique for improvement of the book is gratefully acknowledged.

Newark, NJ, USA — Alluru S. Reddi

Contents

1 Introduction to Acid–Base 1
2 Basic Acid–Base Chemistry and Physiology 7
3 Methods to Assess Acid–Base Disorders 21
4 Acid–Base Disorders: General Considerations and Evaluation 39
5 Lactic Acidosis 63
6 Ketoacidosis 85
7 Toxin-Induced Acid-Base Disorders 103
8 Renal Tubular Acidosis 127
9 Acid–Base Disorders in Gastrointestinal Diseases 157
10 Acid–Base Disorders in Kidney Disease 171
11 Metabolic Alkalosis 185
12 Respiratory Acidosis 213
13 Respiratory Alkalosis 231
14 Mixed Acid–Base Disorders 243
15 Drug-Induced Acid-Base Disorders 257
16 Acid–Base Disorders in Critically Ill Patients 263
17 Acid-Base Disorders in Liver Disease 281
18 Acid-Base Disorders in Total Parenteral Nutrition 293
19 Acid-Base Disorders in Pregnancy 299
20 Acid-Base Disorders in Surgical Patients 305
Index 309

Chapter 1
Introduction to Acid–Base

The arterial blood gas (ABG) determination is an important laboratory test in the evaluation of oxygenation and acid–base status of the body. This ABG test is most frequently done in the emergency department and critical care units. Also, this test is a valuable tool during operative procedures. When an ABG is ordered, four important values are reported: pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), and bicarbonate (HCO_3^-). Base excess (BE) is also reported (see Chap. 3), which is used by some clinicians. The percent saturation of hemoglobin with oxygen in the arterial blood (SaO_2) is done by either direct measurement using CO-oximetry or estimated from pO_2. Only some blood gas analyzers are equipped with CO-oximeter for measurement of SaO_2 directly, and other laboratories report calculated value. Mean SaO_2 is 98%.

Technique of ABG Measurement

After collection of either arterial or venous blood, it is introduced into the blood gas analyzer (BGA). The BGA aspirates the blood into a measuring chamber which contains ion-specific electrodes for pH, pO_2, and pCO_2. The pH is measured by two electrodes: a pH-measuring electrode and a reference electrode. The reference electrode contains a saturated solution of KCl, and the current flow compares the voltage of the unknown blood with a reference voltage, and the difference in voltage is displayed on a voltmeter calibrated in pH units.

pO_2 is measured with Clark electrode or polarographic electrode. O_2 diffuses across polypropylene membrane through the electrode immersed in phosphate buffer. O_2 then reacts with water in the buffer and generates voltage (current) that is proportional to the number of O_2 molecules in the solution. The current is measured and expressed as pO_2.

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_1

The pCO_2 electrode is a modified pH electrode with a silicone or Teflon rubber CO_2 semipermeable membrane covering the tip of the electrode. The electrode is bathed in a solution containing $NaHCO_3$. The CO_2 diffuses from the blood across the semipermeable membrane, and the reaction between CO_2 and water generates free H^+ in proportion to the pCO_2

A brief description of each of these components of ABG is described below.

pH

pH is measured by a specific pH electrode, and it indicates either acidity or alkalinity of blood. Actually the pH is an indirect measurement of hydrogen ion concentration (abbreviated as $[H^+]$).The normal $[H^+]$ in the extracellular fluid is about 40 nmol/L or 40 nEq/L (range 38–42 nmol/L), which is precisely regulated by an interplay between body buffers, lungs, and kidneys. Since many functions of the cell are dependent on the optimum $[H^+]$, it is extremely important to maintain $[H^+]$ in blood ~40 nmol/L. Any deviation from this $[H^+]$ results either in acidemia ($[H^+]$ >40 nmol/L) or alkalemia ($[H^+]$ <40 nmol/L). The $[H^+]$ in blood is so low that it is not measured routinely. However, the $[H^+]$ is measured as pH, which is expressed as:

$$pH = -\log\left[H^+\right] \tag{1.1}$$

Thus, pH is defined as the negative logarithm of the $[H^+]$. An inverse relationship exists between pH and $[H^+]$. In other words, as the pH increases, the $[H^+]$ decreases and vice versa (Table 1.1). Cells cannot function at a pH below 6.8 and above 7.8. The normal arterial pH ranges from 7.38 to 7.42, which translates to a $[H^+]$ of 38–42 nmol/L. Mean pH is 7.40.

Table 1.1 Relationship between pH and $[H^+]$

pH (Units)	$[H^+]$ (nmol/L)
7.90	13
7.80	16
7.70	20
7.60	25
7.50	32
7.40	40
7.30	50
7.20	63
7.10	79
7.00	100
6.90	126
6.80	159
6.70	199
6.60	251

pO_2

pO_2 refers to the partial pressure of oxygen (tension) dissolved in blood. As mentioned, it is measured specifically by a pO_2 electrode. The mean value of pO_2 in a normal young man is approximately 97 mmHg at sea level. Various formulas have been developed to predict approximate values of pO_2 in individuals of varying ages. Clinically, however, it is cumbersome to use these formulas on daily basis. One suggested way of estimating approximate pO_2 is to assume 100 mmHg in a 10-year-old child and a decrease of 5 mmHg for every 10 years up to 90 years of age. For example, a 20-year-old man will have a pO_2 of 95 mmHg, and it is 60 mmHg for a 90-year-old man.

pCO_2

pCO_2 indicates the partial pressure of carbon dioxide (tension) dissolved in blood. It reflects alveolar ventilation and represents respiratory component of ABG. The normal values range from 35 to 46 mmHg with a mean value of 40 mmHg.

HCO_3^-

HCO_3^- represents the bicarbonate concentration ($[HCO_3^-]$) of the blood sample that is sent for the analysis of ABG. It is not a measured value but calculated from Henderson–Hasselbalch equation (see Chap. 2). This calculated $[HCO_3^-]$ is lower by 1–2 mEq/L than the $[HCO_3^-]$ from chemistry panel, which is measured as total CO_2. Total CO_2 comprises three components: HCO_3^-, dissolved CO_2, and carbonic acid. For this reason, total CO_2 concentration is higher than the calculated HCO3$^-$. Total CO_2, calculated HCO_3^-, and base excess (see Chap. 3) are indicators of metabolic components of ABG.

Normal ABG Values

Mean and range values of normal ABG are shown in Table 1.2.

Table 1.2 Mean and range values of normal ABG

Component	Mean	Range
pH	7.40	7.36–7.44
$[H^+]$ (nnol/L)	40	36–44
pO_2 (mmHg)	97	80–100
pCO_2 (mmHg)	40	36–44
$[HCO_3^-]$ (mEq/L)	24	22–26
BE (mEq/L)	0	0 ± 2
SaO_2 (%)	97	97–98

BE base excess, *SaO_2* saturation of hemoglobin with oxygen

Arterial vs. Venous Blood Sample for ABG

Arterial blood is used most of the time to evaluate an acid–base disorder. However, venous blood samples can be used because there is insignificant difference in ABG values between these two samples (Table 1.3).

Although there is not much difference between the two samples in normal individuals, significant difference can be observed in pathological conditions. For example, large arteriovenous difference can be found in a patient with decreased cardiac output and on mechanical ventilation. In such a patient, the arterial pCO_2 remains normal, but central venous pCO_2 may be extremely elevated, as more CO_2 is added to the perfusing tissue. In low cardiac output states, an arterial ABG is useful in assessing pulmonary gas exchange, and central venous ABG is useful in assessing pH and tissue oxygenation.

Primary Acid–Base Disorders

As stated above, a change in plasma [HCO_3^-] results in a metabolic acid–base disturbance, whereas a change in arterial pCO_2 results in a respiratory acid–base disorder. Clinically, four primary acid–base disorders can be recognized: (1) *metabolic acidosis*, (2) *metabolic alkalosis*, (3) *respiratory acidosis*, and (4) *respiratory alkalosis*. Changes in pH, HCO_3^-, and pCO_2 for each primary acid–base disorder are shown in Table 1.4. In addition, the respiratory acid–base disorders are classified into either acute or chronic based on the buffering mechanism. Buffering for acute disorder is complete in minutes to few hours, whereas for chronic disorder complete buffering takes a few days (see Chap. 2). Systemic disorders cause primary acid–base disorders, and the resultant pH changes are minimized by appropriate secondary physiologic response, as shown in Table 1.5.

Table 1.3 Differences between arterial and venous blood samples

ABG value	Arterial blood	Venous blood
pH	7.40	7.36
[H^+] (nmol/L)	40	44
pCO_2 (mmHg)	40	48
[HCO_3^-] (mEq/L)	24	26
pO_2 (mmHg)	~97	~50

Table 1.4 Primary acid–base disturbances

Acid–base disorder	pH	Primary change
Metabolic acidosis	<7.40	↓ HCO_3^-
Metabolic alkalosis	>7.40	↑ HCO_3^-
Respiratory acidosis	<7.40	↑ pCO_2
Respiratory alkalosis	>7.40	↓ pCO_2

↑ increase ↓ decrease

Table 1.5 Primary acid–base disturbances and their secondary response

Acid–base disorder	pH	Primary change	Secondary change	Mechanism of secondary change
Metabolic acidosis	<7.40	↓ HCO_3^-	↓ pCO_2	Hyperventilation
Metabolic alkalosis	>7.40	↑ HCO_3^-	↑ pCO_2	Hypoventilation
Respiratory acidosis	<7.40	↑ pCO_2	↑ HCO_3^-	↑ HCO_3^- reabsorption
Respiratory alkalosis	>7.40	↓ pCO_2	↓ HCO_3^-	↓ HCO_3^- reabsorption

Secondary Physiologic Response (or Compensation)

It is a physiologic process that minimizes changes in pH or $[H^+]$ brought about by a primary change. In clinical practice, the term compensation rather than secondary physiologic response is usually used. Two types of compensatory responses (secondary physiologic responses) are involved: respiratory and renal. In a metabolic acid–base disorder, the compensatory response is respiratory. For example, in metabolic acidosis, the primary change is a decrease in plasma $[HCO_3^-]$ and an increase in $[H^+]$. The compensatory response is a decrease in pCO_2 due to hyperventilation. This decrease in pCO_2 limits the rise in $[H^+]$, and thus the pH is returned to normal. The observed hyperventilation represents the normal physiologic response to an increase in $[H^+]$. Conversely, hypoventilation is an appropriate physiological response to metabolic alkalosis. In a respiratory acid–base disorder, the compensatory response is renal. In respiratory acidosis, the primary change is an increase in pCO_2 and a decrease in pH or an increase in $[H^+]$. The renal compensation increases the plasma $[HCO_3^-]$ with a resultant increase in pH close to normal. Six "rules of thumb" were introduced to calculate the extent of compensatory response to the primary acid–base disorder (see Table 1.5).

Factors Influencing ABG

Factors such as collection of blood, time to collection of blood and its transportation to the laboratory, and temperature will influence the ABG results. Arterial blood should be collected under anaerobic conditions without air bubbles. Air bubbles give high pO_2, and the blood samples should be placed in ice immediately. At 4 °C, ABG values remain stable for 2–4 h. Another reason for immediate determination of ABG is to prevent continuous metabolism occurring in white blood cells (WBCs) and reticulocytes. During metabolism, O_2 is consumed and CO_2 is generated. As a result, a decrease in pO_2 and an increase in pCO_2 up to 5 mmHg can occur. Because of an increase in pCO_2, blood pH may be lower by 0.05 units. ABG should be determined immediately in patients with high WBC count (>12,000) because of high consumption of O_2 during metabolism in these cells.

Too much anticoagulant such as heparin may lower pH, pO_2, and pCO_2. Citrate may decrease pH.

Table 1.6 Effect of temperature on ABG

Temperature (C)	pH	pO_2 (mmHg)	pCO_2 (mmHg)
37	7.40	80	40
30	7.50	51	30
35	7.43	70	37
39	7.37	91	44

Changes in body temperature affect ABG results. In the ABG analyzer, the samples are read at a temperature of 37^0 C. Deviations from this temperature, either decrease or increase, result in changes in pH, pO_2, and pCO_2. Table 1.6 shows temperature-corrected values for a normal ABG.

Suggested Reading

Adrogué HJ, Madias NE. Measurement of acid-base status. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 775–88.

Ashwood ER, Kost G, Kenny M. Temperature correction of blood-gas and pH measurements. Clin Chem. 1983;29:1877–85.

Byrne AL, Bennett M, Chatterji R, et al. Peripheral venous and arterial blood gas analysis in adults: are they comparable? A systemic review and meta-analysis. Respirology. 2014;19:168–75.

Hasan A. Handbook of blood gas/acid-base interpretation. London: Springer; 2013.

Kelly A-M. Review article: can venous blood gas analysis replace arterial in emergency medical care. Emerg Med Australia. 2010;22:493–8.

Malley WJ. Clinical blood gases. Application and noninvasive alternatives. Philadelphia: WB Saunders; 1990.

Neufeld O, Smith JR, Goldman SL. Arterial oxygen tension in relation to age in hospitalized patients. J Am Geriatr Soc. 1973;XXI:4–9.

Chapter 2
Basic Acid–Base Chemistry and Physiology

As discussed in Chap. 1, the acid–base physiology deals with the maintenance of normal hydrogen ion concentration ($[H^+]$) and pH in body fluids and is precisely regulated by an interplay between body buffers, lungs, and kidneys. In everyday life, the blood pH is under constant threat by endogenous acid and base loads. If not removed, these loads can cause severe disturbances in blood pH and thus impair cellular function. However, three important regulatory systems prevent changes in pH and thus maintain blood pH in the normal range. These protective systems, as stated, are buffers, lungs, and kidneys.

Production of Endogenous Acids and Bases

An acid is a proton donor, whereas a base is a proton acceptor. Under physiological conditions, the diet is a major contributor to endogenous acid and base production.

Endogenous Acids

The oxidation of dietary carbohydrates, fats, and amino acids yields CO_2. About 15,000 mmol of CO_2 are produced by cellular metabolism daily. This CO_2 combines with water in the blood to form carbonic acid (H_2CO_3):

$$CO_2 + H_2O \overset{CA}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_3^-. \tag{2.1}$$

This reaction is catalyzed by carbonic anhydrase (CA), an enzyme present in tissues and red blood cells but absent in plasma. When H_2CO_3 dissociates into CO_2 and

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_2

H_2O (a process called dehydration), the CO_2 is eliminated by the lungs. For this reason, H_2CO_3 is called a *volatile acid*. In addition to volatile acid, the body also generates *nonvolatile (fixed) acids* from cellular metabolism. These nonvolatile acids are produced from sulfur-containing amino acids (i.e., cysteine and methionine) and phosphoproteins. The acids produced are sulfuric acid and phosphoric acid, respectively. Other sources of endogenous nonvolatile acids include glucose, which yields lactic and pyruvic acids; triglycerides, which yield acetoacetic and β-hydroxybutyric acids (ketoacids); and nucleoproteins, which yield uric acid. Hydrochloric acid is also formed from the metabolism of cationic amino acids (i.e., lysine, arginine, and histidine). Sulfuric acid accounts for 50% of all acids produced. A typical North American diet produces 1 mmol/kg/day of endogenous nonvolatile acid. Under certain conditions, acids are produced from sources other than the diet. For example, starvation produces ketoacids, which can accumulate in the blood. Similarly, strenuous exercise generates lactic acid. Drugs such as corticosteroids cause endogenous acid production by enhancing catabolism of muscle proteins.

Endogenous Bases

Endogenous base (HCO_3^-) is generated from anionic amino acids (glutamate and aspartate) in the diet. Also, citrate or lactate generated during metabolism of carbohydrate yields HCO_3^-. Vegetarian diets contain high amounts of anionic amino acids and small amounts of sulfur and phosphate-containing proteins. Therefore, these diets generate more base than acid. In general, the production of acid exceeds that of base in a person ingesting a typical North American diet. Table 2.1 summarizes endogenous sources of acids and bases in normal individuals.

Table 2.1 Sources of acid and alkali production

Source	Acid produced	Alkali produced
Sulfur-containing amino acids (cysteine, cystine, methionine)	Sulfuric acid (H_2SO4)	
Phosphoproteins, phospholipids	Phosphoric acid (H_2PO_4)	
Glucose	Lactic acid, pyruvic acid	
Triglycerides	Acetoacetic acid, β-hydroxybutyric acid	
Nucleoproteins	Uric acid	
Organic cations	HCl	
Diet with anionic amino acids (glutamate, aspartate)		HCO_3^-
Citrate, lactate		HCO_3^-

Maintenance of Normal pH

Buffers

All acids that are produced must be removed from the body in order to maintain normal blood pH. Although the kidneys eliminate most of these acids, it takes hours to days to complete the process. Buffers (both cellular and extracellular) are the first line of defense against wide fluctuations in pH. The most important buffer in blood is bicarbonate/carbon dioxide (HCO_3^-/CO_2). Other buffer systems are disodium phosphate/monosodium phosphate ($Na_2HPO_4^{2-}/NaH_2PO_4^-$) and plasma proteins. In addition, erythrocytes contain the important hemoglobin (Hb) system, reduced Hb (HHb^-) and oxyhemoglobin (HbO_2^{2-}). Bones also participate in buffering. The HCO_3^-/CO_2 system provides the first line of defense in protecting pH. Its role as a buffer can be described by incorporating this system into the Henderson–Hasselbalch equation as follows:

$$\mathrm{pH} = \mathrm{pKa} + \log \frac{\left[\mathrm{HCO_3^-}\right]}{\left[\mathrm{H_2CO_3}\right]}. \tag{2.2}$$

Although H_2CO_3 cannot be measured directly, its concentration can be estimated from the partial pressure of CO_2 (pCO_2) and the solubility coefficient (α) of CO_2 at known temperature and pH. At normal temperature of 37 °C and pH of 7.4, the pCO_2 is 40 mmHg, α is 0.03, and pK_a is 6.1. The Henderson–Hasselbalch equation can be appropriately written as:

$$\mathrm{pH} = 6.1 + \log \frac{\left[\mathrm{HCO_3^-}\right]}{0.03 + \mathrm{pCO_2}}. \tag{2.3}$$

Normal plasma $[HCO_3^-]$ is 24 mEq/L. Therefore,

$$\begin{aligned} \mathrm{pH} &= 6.1 + \log \frac{24}{0.03 \times 40} \\ \mathrm{pH} &= 6.1 + \log \frac{24}{1.2} = 6.1 + \log \frac{20}{1} \\ \mathrm{pH} &= 6.1 + 1.3 = 7.40 \end{aligned} \tag{2.4}$$

It should be noted from the Henderson–Hasselbalch equation that the pH of a solution is determined by the pK_a and the ratio of $[HCO_3^-]$ to pCO_2, and not by their absolute values. Thus, because the kidneys regulate the $[HCO_3^-]$ and the lungs pCO_2, the kidneys and lungs determine the pH of extracellular fluids.

Phosphate buffers are effective in regulating intracellular pH more efficiently than extracellular pH. Their increased effectiveness intracellularly is due to their

higher concentrations inside the cell. Also, the pK_a of this system is 6.8, which is close to the intracellular pH.

Plasma proteins contain several ionizable groups in their amino acids that buffer either acids or bases. For example, the imidazole groups of histidine and the N-terminal amino groups have pK_a that are close to extracellular pH and thus function as effective buffers. In blood, hemoglobin is an important protein buffer because of its abundance in red blood cells.

Extracellular buffering to an acid load is complete within 30 min. Subsequent buffering occurs intracellularly and takes several hours to complete. Most of this intracellular buffering occurs in bone. Bone becomes an important source of buffering acid load acutely by an uptake of H^+ in exchange for Na^+, K^+, and bone minerals. These bone minerals rescue the HCO_3^-/CO_2 system in severe acidosis.

It is apparent from the Henderson–Hasselbalch Eq. 2.2 that any change either in $[HCO_3^-]$ or pCO_2 can cause a change in blood pH. The acid–base disturbance that results from a change in plasma $[HCO_3^-]$ is termed a *metabolic acid–base disorder* whereas that due to a change in pCO_2 is called a *respiratory acid–base disorder*.

Lungs

After buffers, the lungs are the second line of defense against pH disturbance. In a normal individual, pCO_2 is maintained around 40 mmHg. This pCO_2 is achieved by expelling the CO_2 that is produced by cellular metabolism through the lungs. Any disturbance in the elimination of CO_2 may cause a change in blood pH. Thus, alveolar ventilation maintains normal pCO_2 to prevent an acute change in pH. Alveolar ventilation is controlled by chemoreceptors located centrally in the medulla and peripherally in the carotid body and aortic arch. Blood $[H^+]$ and pCO_2 are important regulators of alveolar ventilation. The chemoreceptors sense the changes in $[H^+]$ or pCO_2 and alter alveolar ventilatory rate. For example, an increase in $[H^+]$, i.e., a decrease in pH, stimulates ventilatory rate and decreases pCO_2. These responses, in turn, raise pH (see Eq. 2.3). Conversely, a decrease in $[H^+]$ or an increase in pH depresses alveolar ventilation and causes retention of pCO_2 so that the pH is returned to near normal. An increase in pCO_2 stimulates ventilatory rate, whereas a decrease depresses the ventilatory rate. The respiratory response to changes in $[H^+]$ takes several hours to complete.

Kidneys

As stated earlier, 1 mmol/kg/day of fixed acid is produced from the diet. If not removed, this acid is retained and plasma $[HCO_3^-]$ decreases. The result is metabolic acidosis. In a healthy individual, metabolic acidosis does not occur because

the kidneys excrete the acid load and maintain plasma [HCO_3^-] around 24 mEq/L. The maintenance of [HCO_3^-] is achieved by three renal mechanisms:

1. Reabsorption of filtered HCO_3^-
2. Generation of new HCO_3^- by titratable acid (TA) excretion
3. Formation of HCO_3^- from generation of NH_4^+

Reabsorption of Filtered HCO_3^-

HCO_3^- is freely filtered at the glomerulus. The daily filtered load (plasma concentration × glomerular filtration rate) of HCO_3^- is 4320 mEq (24 mEq/L × 180 L/day = 4320 mEq/day). Almost all of this HCO_3^- is reabsorbed by the tubular segments of the nephron, and urinary excretion is negligible (< 3 mEq). HCO_3^- reabsorption by various segments of the nephron can be summarized as follows:

- Proximal tubule: 80%.
- Loop of Henle: 10%.
- Distal tubule: 6%.
- Collecting duct: 4%.

Proximal Tubule

As stated earlier, the proximal tubule has a high capacity for HCO_3^- reabsorption. This reabsorption occurs because of H^+ secretion into the tubular lumen via the Na/H exchanger isoform 3 (NHE3), as shown in Fig. 2.1. Another transporter, called H-ATPase, is also responsible for transport of some protons into the lumen (see Fig. 2.1). The H^+ combines with the filtered HCO_3^- to form H_2CO_3. The apical membrane is rich in carbonic anhydrase IV, which splits H_2CO_3 into H_2O and CO_2. The CO_2 diffuses into the cell where it is hydrated to form H_2CO_3 in the presence of carbonic anhydrase II. H_2CO_3 is dehydrated to form H^+ and HCO_3^-. H^+ are subsequently secreted into the lumen via the Na/H exchanger and H-ATPase to start the cycle again.

HCO_3^- exit across the basolateral membrane occurs via an Na/HCO_3 cotransporter, in which two to three HCO_3^- ions are transported for each Na^+ ion. Another mechanism occurs through the Cl/HCO_3 antiporter, in which one HCO_3^- is exchanged for one Cl^-. Both the energy and electrochemical gradient for H^+ secretion and HCO_3^- exit are provided by the Na/K-ATPase pump located in the basolateral membrane (not shown in Fig. 2.1).

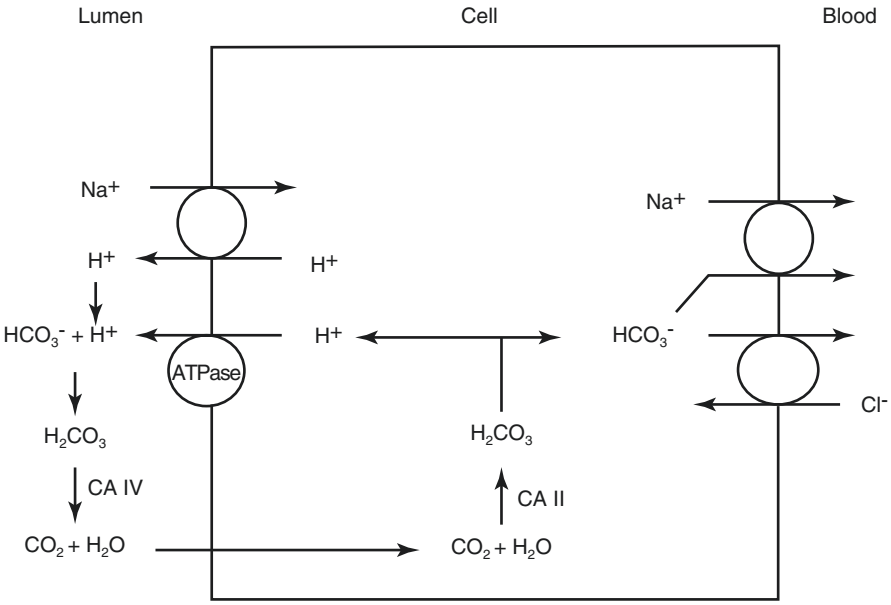

Fig. 2.1 Schematic representation of H^+ secretion and HCO_3^- reabsorption in the proximal tubule cell. CA II carbonic anhydrase II; CA IV carbonic anhydrase IV

Loop of Henle

Most HCO_3^- reabsorption occurs in the thick ascending Henle's loop. The mechanisms for H^+ secretion into the lumen and HCO_3^- exit across the basolateral membrane appear to be similar to those described for the proximal tubule.

Distal Tubule

For the purpose of understanding HCO_3^- reabsorption, it is helpful to divide the distal tubule into three distinct segments: (1) distal convoluted tubule, (2) connecting tubule, and (3) cortical collecting duct. Very little is known about H^+ secretion and HCO_3^- reabsorption in the distal convoluted tubule. This tubule consists of only one cell type, which contains H-ATPase in its apical membrane. The other two segments of the distal tubule consist of principal cells and intercalated cells. The latter cells are responsible for acid–base transport. The intercalated cells in the cortical collecting duct are of three types: type A, type B, and type C cells. Type A intercalated cells contain H-ATPase and K/H exchanger in the apical membrane. H^+ that is formed inside the cell from dehydration of H_2CO_3 is secreted into the lumen by these transporters (Fig. 2.2). HCO_3^- exit is facilitated by the Cl/HCO_3 exchanger.

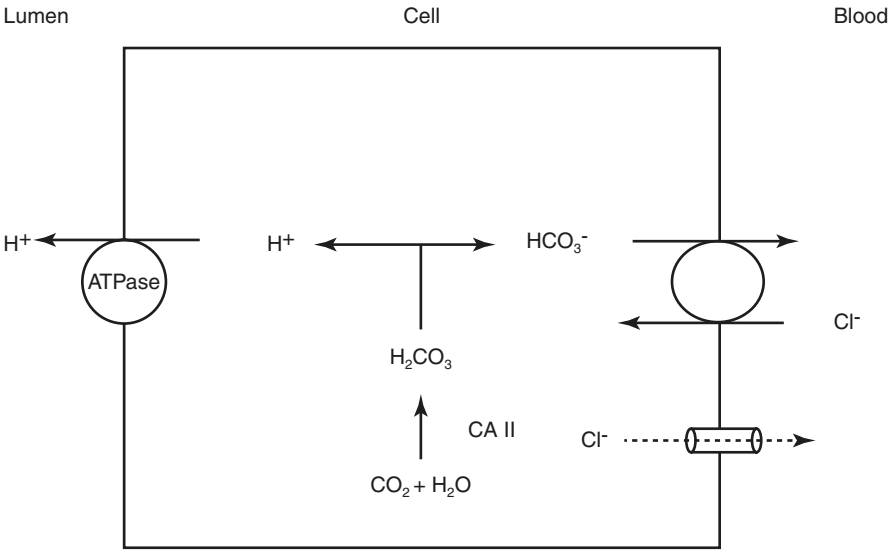

Fig. 2.2 Cellular model for H^+ secretion and HCO_3^- reabsorption in type A intercalated cell of the cortical collecting duct. CA II carbonic anhydrase II; *broken arrow* represents a conductance channel

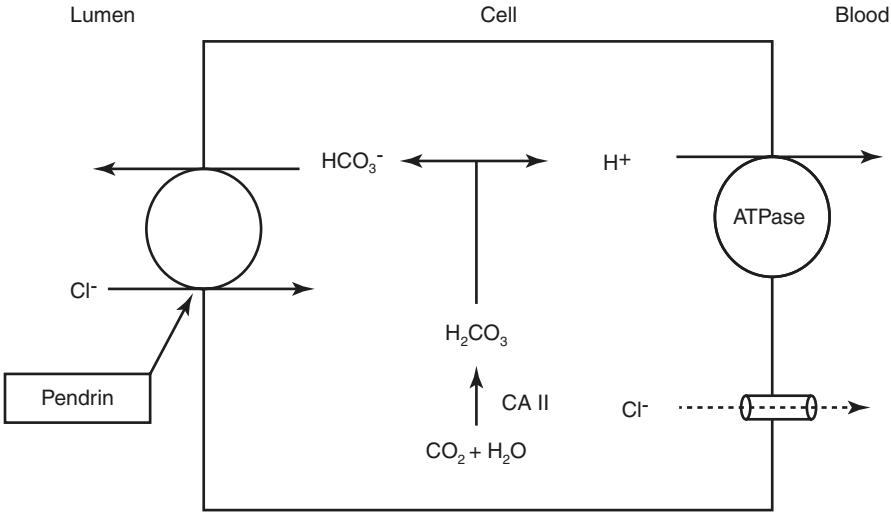

Fig. 2.3 Cellular model for HCO_3^- secretion and H^+ reabsorption in type B intercalated cell of the cortical collecting duct. CA II carbonic anhydrase II; *broken arrow* represents a conductance channel

In contrast, type B intercalated cells secrete HCO_3^- into the lumen (Fig. 2.3). These cells possess pendrin, a Cl/HCO_3 exchanger, in the apical membrane and H-ATPase in the basolateral membrane. HCO_3^- secretion is stimulated by alkali loading and inhibited by depletion of luminal Cl^-.

Type C (formerly non A, non B) cells express H-ATPase and pendrin (Cl/HCO_3 exchanger) in the apical membrane. These cells also participate in HCO_3^- handling.

Collecting Duct

The collecting duct includes the cortical portion and outer and inner medullary portions. The cellular mechanisms of HCO_3^- reabsorption in the cortical collecting duct have been discussed in the previous paragraph. The intercalated cells of the outer medullary and inner medullary collecting duct reabsorb HCO_3^- and secrete protons similar to the type A cell mechanisms (see Fig. 2.2). The cells of outer medullary and inner medullary collecting duct do not secrete HCO_3^- into the lumen.

Regulation of HCO_3^- Reabsorption

A number of factors influence HCO_3^- reabsorption both in the proximal tubule and distal segments of the nephron. These factors are summarized in Tables 2.2 and 2.3. Since the Na/H antiporter is the major mechanism for H^+ secretion, any factor that enhances or inhibits this antiporter stimulates or decreases HCO_3^- reabsorption.

Table 2.2 Factors affecting HCO_3^- reabsorption (or H^+ secretion) by the proximal tubule

Factor	HCO_3^- reabsorption	Possible mechanism
Increase in filtered load of HCO_3^-	↑	Glomerulotubular balance (G-T) is maintained so that a constant fraction of filtered load of HCO_3^- is reabsorbed
Volume contraction	↑	Promotes HCO_3^- reabsorption by ↑ Na/H exchange
Hypokalemia	↑	↓ Intracellular pH increases $[H^+]$ and promotes proton secretion by stimulation of Na/H antiporter
↑ pCO_2	↑	↓ Intracellular pH and ↑ Na/H antiporter
↑Plasma $[H^+]$	↑	↓ Intracellular pH and ↑ Na/H antiporter
Cl^- depletion	↑	↓ Volume and GFR
Hypercalcemia	↑	Probable ↓ volume and GFR
Volume expansion	↓	↑ GFR. Although G–T balance is maintained, still some HCO_3^- escapes from reabsorption
PTH	↓	Probable ↑ in cytosolic Ca^{2+}. No effect on GFR
↓ pCO_2	↓	↑ intracellular pH
Hypophosphatemia	↓	↑ intracellular pH
Acetazolamide	↓	↓ carbonic anhydrase activity

↑ increase ↓ decrease

Table 2.3 Factors affecting HCO_3^- reabsorption by the distal tubule

Factor	HCO_3^- reabsorption	Possible mechanism
Aldosterone	↑	↑ H^+ secretion
↑ pCO_2	↑	↓ Intracellular pH
↑ Plasma [H^+]	↑	↓ Intracellular pH
Impermeant anions (sulfate, phosphate)	↑	↑ H^+ excretion
Hypokalemia (man and rat)	↑	↓ GFR
↓ pCO_2	↓	↑ Intracellular pH
↓ Plasma [H^+]	↓	↑ Intracellular pH
Adrenalectomy	↓	↓H^+ secretion

↑ increase ↓ decrease

Aldosterone plays an important role in HCO_3^- reabsorption and H^+ secretion by the intercalated (type A) cell. It also stimulates Na^+ reabsorption by the principal cell. As a result of this Na^+ reabsorption, the lumen becomes electrically negative, which promotes H^+ secretion. Aldosterone seems to have little effect on HCO_3^- reabsorption in the proximal tubule.

Generation of New HCO_3^- from Excretion of Titratable Acid

Generally, one HCO_3^- ion is reclaimed for each H^+ that is secreted into the lumen. This mechanism alone does not replenish the HCO_3^- lost in buffering the daily acid load. Additional HCO_3^- has to be generated. How does the new HCO_3^- form? The answer is as follows: whenever an H^+ is secreted into the tubule, it combines with the filtered HCO_3^- or with two important urinary buffers, namely, HPO_4^{2-} and NH_3, to form $H_2PO_4^-$ and NH_4^+, respectively. For each H^+ that combines with HPO_4^{2-}, one new HCO_3^- is formed and reabsorbed. The process is different when NH_3 is converted into NH_4^+. In this conversion, HCO_3^- is produced from glutamine metabolism. This process is discussed in the next section. In addition to the generation of new HCO_3^-, the urinary buffers also help to maintain acid urine pH (i.e., 4.5–6.0). If these buffers did not exist, the daily acid load would be excreted into the urine, and its pH would be < 4.5. The amount of free H^+ in the urine is about 0.04 mmol/L. In the absence of urinary buffers, an individual has to excrete 1750 L of urine to eliminate 70 mmol/L of acid load. Obviously, this amount of urine excretion is impossible. Let us now see how urinary buffers replenish the HCO_3^- load.

As mentioned previously, the two major urinary buffers are $HPO_4^{2-}/H_2PO_4^-$ and NH_3/NH_4^+. About 40% of H^+ is excreted as phosphate and the remaining 60% as ammonium. The contribution of phosphate to urinary acid excretion is termed *titratable acidity*, which is defined as the number of equivalents of hydroxyl ions required to titrate a unit volume of acidic urine to the pH of the blood (i.e., pH of 7.40). Thus, the amount of hydroxyl ions used in the titration is equal to the amount of H ions that were buffered in the tubular lumen. If 30 mmol of hydroxyl ions are used to

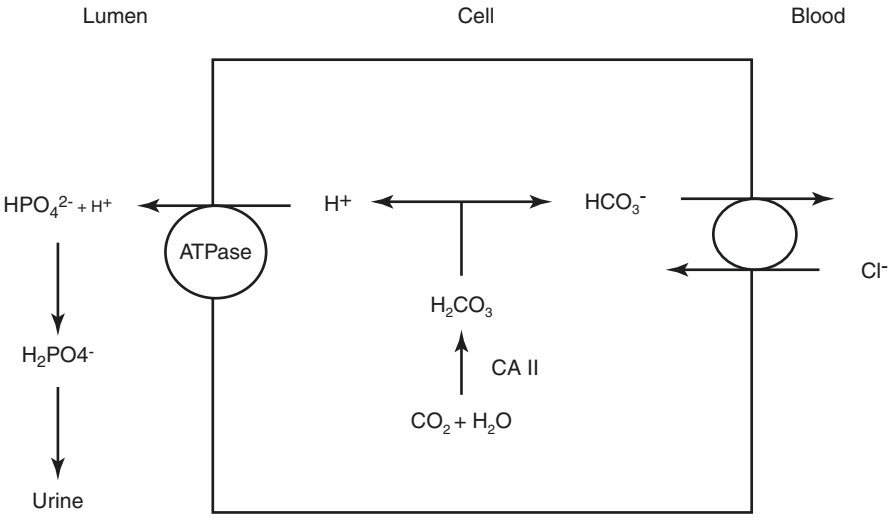

Fig. 2.4 Schematic representation for titratable acid formation in the collecting duct cell. CA carbonic anhydrase

raise urine pH to 7.40, then 30 mmol of H ions are titrated, and 30 mmol of HCO_3^- are generated. Other organic substances, such as creatinine and urate, also contribute to TA excretion to a minor degree. Compared to creatinine and urate, the phosphate buffer pair has a pK_a of 6.8 and thus appears to be an ideal urinary buffer. Figure 2.4 shows the mechanisms by which TA excretion occurs in the collecting duct cell. The filtered phosphate (HPO_4^{2-}) combines with the H^+ secreted in the lumen via H-ATPase to form $H_2PO_4^-$. The H ions are formed inside the cell due to dehydration of H_2CO_3 by the catalytic action of carbonic anhydrase II. Note that one HCO_3^- ion is formed for each H^+ secreted.

Generation of HCO_3^- from NH_4^+

Ammonia exists in two forms: NH_3 and NH_4^+. At physiologic pH of 7.40, most of the ammonia exists in the form of NH_4^+, and < 2% exists as NH_3. This NH_3/NH_4^+ system is important in the generation of new HCO_3^-. The following steps explain how HCO_3^- is generated from NH_4^+.

1. NH_4^+ is formed from metabolism of amino acids (see Chap. 17). Most of this NH_4^+ is used for urea synthesis. This urea has no significant effect on acid–base balance. However, part of this NH_4^+ is used for glutamine synthesis. Glutamine is filtered at the glomerulus and reabsorbed completely in the proximal tubule. In mitochondria of the proximal tubule, glutamine is converted into glutamate and NH_4^+ (Fig. 2.5). This reaction is catalyzed by an enzyme called

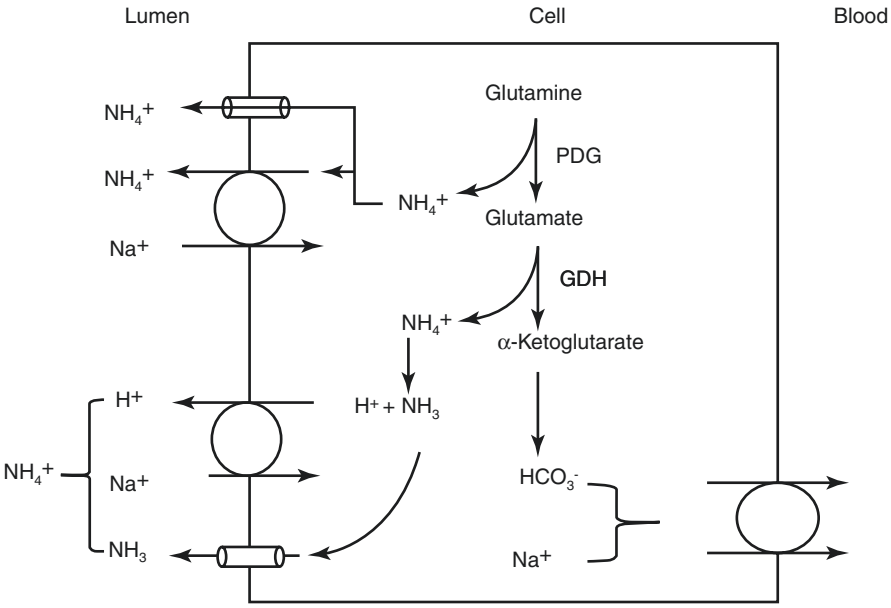

Fig. 2.5 Ammonia (NH_3/NH_4^+) production in the proximal tubule. PDG phosphate-dependent glutaminase; GDH glutamate dehydrogenase

phosphate-dependent glutaminase. Glutamate is further metabolized to α-ketoglutarate and NH_4^+. The enzyme responsible for this conversion is glutamate dehydrogenase. The α-ketoglutarate produced in the reaction is converted to HCO_3^-. The net result of glutamine metabolism is the formation of two NH_4^+ and two HCO_3^- ions. The exit of HCO_3^- through basolateral membrane occurs via Na/HCO_3 cotransporter

2. If this HCO_3^- returns to the general circulation, it is taken up by the liver and used for urea synthesis, which does not have any effect on acid–base balance. The only way ammoniagenesis generates new HCO_3^- from renal glutamine is to excrete NH_3 in the form of NH_4^+ as urinary buffer. Note that secretion of one H^+ generates one HCO_3^- ion. Once this new HCO_3^- is regenerated, it returns to the extracellular fluid and functions as a buffer
3. In order for the NH_4^+ to be excreted in the urine, it has to be secreted and transported from the proximal tubule to the cortical collecting duct. Secretion of NH_4^+ into the lumen of the proximal tubule occurs by three important mechanisms (Fig. 2.5): (1) barium-sensitive NH_4^+ conductance channel (mediated by K channel); (2) Na/NH_4 exchanger (mediated by Na/H exchanger isoform 3 or NHE3); and (3) Na/H exchanger3. Also, passive diffusion of NH_3 occurs due to pH gradient between the lumen and cell. Lumen pH is much lower than cell pH. In the lumen, NH_3 combines with the secreted H^+ to form NH_4^+. HCO_3^- exits via Na/HCO_3 cotransporter in the ratio of 1:3

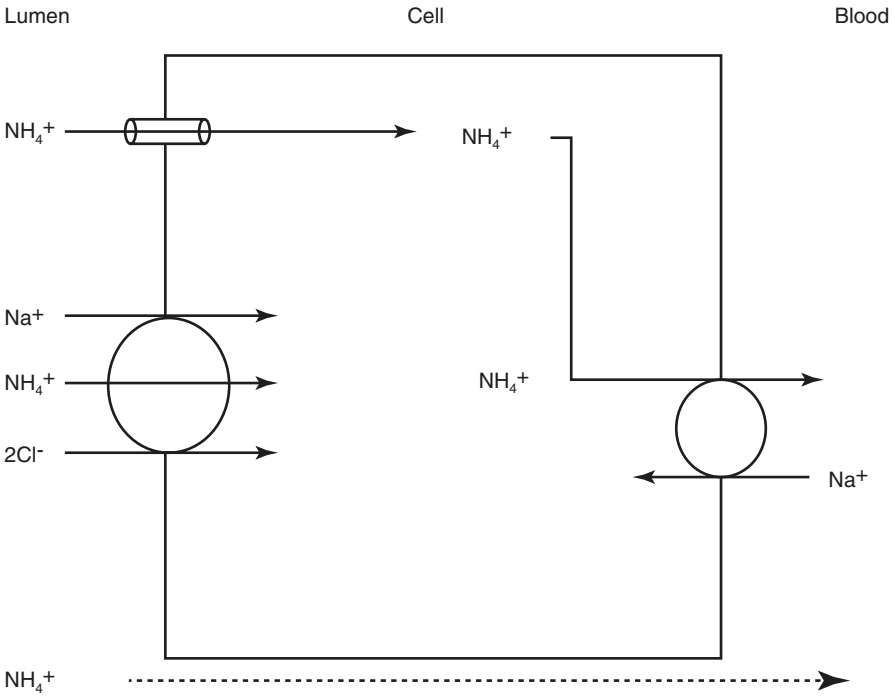

Fig. 2.6 NH_4^+ transport in thick ascending limb of Henle's loop

4. NH_4^+ from the proximal tubule reaches the thick ascending limb of Henle's loop (TALH) where 40–80% is reabsorbed. Unlike other segments of the nephron, the TALH is impermeable to NH_3. In the TALH, NH_4^+ is transported from the lumen to cell by three mechanisms (Fig. 2.6). First, NH_4^+ enters cells by replacing K^+ on Na/K/2 Cl cotransporter. This is the major mechanism of NH_4^+ transport. Second, NH_4^+ entrance is facilitated by barium-sensitive K channel, and finally, NH_4^+ moves passively across the paracellular pathway that is facilitated by lumen-positive voltage gradient. NH_4^- exits the basolateral membrane via Na/H exchanger mediated by NHE4 as Na/NH_4
5. Once NH_4^+ enters the TALH, it accumulates in the medullary interstitium. The pH of the medullary interstitium is slightly alkaline, and NH_4^+ dissociates into NH_3 and H^+. If this NH_3 diffuses back into the blood, excretion of NH_4^+ into the urine is diminished. This backleak of NH_3 is prevented by its recirculation in the medullary interstitium. The descending and ascending limbs of Henle's loop are shown to participate in this recycling as a countercurrent multiplication system. This recycling of NH_3/NH_4^+ serves two major functions: (1) maintenance of high medullary concentration of NH_3/NH_4^+ and (2) prevention of NH_3 diffusion into the blood

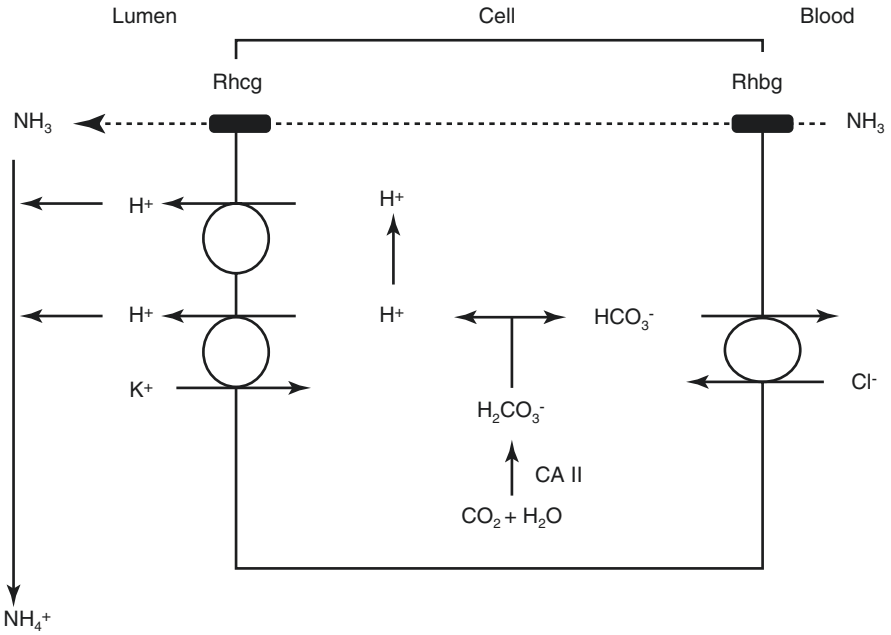

Fig. 2.7 Ammonia secretion and formation of NH_4^+ as urinary buffer in the cortical collecting duct

6. A small fraction of medullary NH_4^+ enters the late proximal tubule, and the rest enters the cortical collecting duct. Cortical collecting duct is the major segment of the nephron that secretes and excretes 80% of NH_4^+ in the urine. NH_4^+ secretion into the lumen occurs by parallel NH_3 and H^+ secretion without significant transepithelial transport of NH_4^+. This NH_3 comes directly from the interstitium, which is transported by ammonia transporters called rhesus-associated glycoproteins A, B, and C (abbreviated as Rhag, Rhbg, and Rhcg, respectively). Only Rhbg and Rhcg are involved in the human kidney (Fig. 2.7). H^+ are derived from dissociation of H_2CO_3 formed from CO_2 and water in the presence of carbonic anhydrase II (Fig. 2.7). These H^+ are secreted into the lumen via H-ATPase and K/H exchanger (Fig. 2.7). NH_4^+ is formed in the lumen by combination of NH_3 and H^+ and is excreted in the urine. A number of factors influence NH_4^+ synthesis and its excretion, as shown in Table 2.3

Net Acid Excretion (Urinary Acidification)

As stated previously, the H ions that are generated as fixed acids must be excreted daily in the urine to maintain normal acid–base balance. These H^+ are not excreted as free ions. Instead, they are excreted in the form of TA and NH_4^+. Only a small amount of H^+ is excreted as free ions. Each liter of urine contains approximately

Table 2.3 Conditions regulating NH_4^+ synthesis and its excretion

Conditions	Synthesis	Excretion
Metabolic acidosis	↑	↑
Metabolic alkalosis	↓	↓
High urine pH	↓ (?)	↓
Low urine pH	↑ (?)	↑
High glutamine delivery	↑	↑
Low glutamine delivery	↓	↓
High urine flow	–	↑
Hypokalemia	↑	↑
Hyperkalemia	↓	↓
Mineralocorticoids	↑	↑
Glucocorticoids	↑	↑

↑ increase ↓ decrease

0.04 mmol of free H^+. Because of this negligible amount of free H^+, the urine pH is maintained between 4.5 and 6.0. Another reason for the maintenance of acid urine pH is the relatively low concentration of HCO_3^- (<3 mEq/L of urine). Urinary loss of HCO_3^- greater than 5 mEq would generally raise the pH above 6.0 and make the urine alkaline. HCO_3^- loss in the urine is generally equated as a gain of H^+ to the body.

The excretion of H^+ as TA and NH_4^+ is quantified as *net acid excretion* (NAE). NAE is defined as the sum of TA and NH_4^+ minus any H^+ that is added to the body because of urinary loss of HCO_3^-. Therefore, NAE is calculated as follows:

$$\text{NAE} = \text{TA} + \text{NH}_4^+ - \text{HCO}_3^-.$$

Metabolic acidosis increases the NAE because the excretion of both TA and NH_4^+ increases. Thus, NAE reflects the amount of H^+ excretion in the form of urinary buffers.

Suggested Reading

DuBose TD. Disorders of acid-base balance. In: Skorecki K, et al., editors. Brenner & Rector's the kidney. 10th ed. Philadelphia: Elsevier; 2016. p. 511–58.

Hamm LL. Renal regulation of hydrogen ion balance. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid–base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 79–117.

Hamm LL, Nakhoul N, Hering-Smith KS. Acid-base homeostasis. Clin J Am Soc Nephrol. 2015;10:2232–42.

Palmer BF. Normal acid-base balance. In: Johnson RJ, Feehally J, Floege J, editors. Comprehensive clinical nephrology. 5th ed. Philadelphia: Mosby; 2015. p. 142–8.

Weiner ID, Verlander JW. Renal ammonia metabolism and transport. Compr Physiol. 2013;3:201–20.

Weiner ID, Verlander JW, Wingo CS. Renal acidification mechanisms. In: Mount DB, Sayegh MH, Singh AK, editors. Core concepts in the disorders of fluid, electrolytes and acid–base balance. New York: Springer; 2013. p. 203–33.

Weiner D, Verlander JW. Ammonia transporters and their role in acid-base balance. Physiol Rev. 2017;97:465–94.

Chapter 3
Methods to Assess Acid–Base Disorders

Acid–base disorders are extremely common in critically ill patients. They carry increased morbidity and mortality. Therefore, accurate assessment and appropriate therapeutic intervention are necessary to prevent these associated complications.

Three methods (approaches) of assessing acid–base disorders have been developed by several investigators. These are:

1. Physiologic (traditional or bicarbonate-based) method
2. Base excess method
3. Physicochemical (Quantitative) method

This chapter assesses and discusses both merits and drawbacks of each one of these methods in detail.

Physiologic Method

The physiologic method is based on BrØnsted–Lowry's definition of acids and bases and on bicarbonate–carbon dioxide (HCO_3^-/CO_2) buffer system. Acid is defined as a proton (H^+) donor and base is a proton acceptor. Historically, Henderson in 1908 [1–3] recognized the importance of this buffer system in neutralizing excess acid in the body. Following the law of mass action, he subsequently derived the landmark equation for calculating $[H^+]$ as follows:

$$\left[H^+\right] = \frac{K \times \left[CO_2\right]}{\left[HCO_3^-\right]} \tag{3.1}$$

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_3

With the introduction of pH by Sörenson in 1912 [1, 2], Henderson's equation was modified by Hasselbalch in 1916 [1, 2], as follows:

$$\mathrm{pH} = \mathrm{pKa} + \log \frac{\left[\mathrm{HCO_3^-}\right]}{\left[\mathrm{H_2CO_3}\right]} \tag{3.2}$$

where H_2CO_3 is carbonic acid. This equation became known as Henderson–Hasselbalch equation and is being taught in acid–base physiology ever since.

The supply of H^+ and HCO_3^- is unlimited as long as the availability of pCO_2 is normal. Initially CO_2 combines with water to form H_2CO_3, which dissociates (ionizes) into H^+ and HCO_3^- (as discussed in Chap. 2). At pH of 7.40, most of the dissolved CO_2 is maintained as HCO_3^-, as shown below:

$$\mathrm{CO_2 + H_2O \overset{CA}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_3^-}. \tag{3.3}$$

This reaction is catalyzed by carbonic anhydrase (CA) and is extremely important in biologic fluids because of formation of not only HCO_3^- but also $[H^+]$ and thus plays an important role in acid–base physiology.

Based on Henderson–Hasselbalch Eq. 3.2, *four* primary acid–base disorders, as discussed in Chap. 1, have been introduced. In addition, the respiratory acid–base disorders are classified into either acute or chronic based on the buffering mechanism. Buffering for acute disorder is completed in minutes to few hours, whereas for chronic disorder complete buffering takes a few days. Systemic disorders cause primary acid–base disorders, and the resultant pH changes are minimized by appropriate secondary physiologic response, as shown in Table 3.1.

Anion Gap

The introduction of anion gap (AG) has largely improved the interpretation of acid–base disorders by the physiologic approach. The AG elucidates, in particular, the cause of metabolic acidosis. Full discussion of AG is presented in Chap. 4. It

Table 3.1 Normal compensatory responses to primary acid–base disorders

Acid–base disorder	Compensatory response
Metabolic acidosis	$pCO_2 = HCO_3 \times 1.5 + 8 \pm 2$ or for each mEq/L decrease in HCO_3^-, pCO_2 decreases by 1.2 mmHg
Metabolic alkalosis	For each mEq/L increase in HCO_3^-, pCO_2 increases by 0.7 mmHg
Respiratory acidosis	
Acute	For each mmHg increase in pCO_2, HCO_3^- increases by 0.1 mEq/L
Chronic	For each mmHg increase in pCO_2, HCO_3^- increases by 0.4 mEq/L
Respiratory alkalosis	
Acute	For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.2 mEq/L
Chronic	For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.4 mEq/L

signifies the presence of unexplained anions, such as the presence of organic acids. Normal AG varies between 3 and 11 mEq/L. Patients with metabolic acidosis may have normal, high, or low AG. Generally AG is influenced by the levels of albumin; therefore, the AG should be corrected for hypo- or hyperalbuminemia. Since critically ill patients have hypoalbuminemia, uncorrected AG may lead to misdiagnosis.

Another concept that is useful in the evaluation of physiologic acid–base disorder is $\triangle AG/\triangle HCO_3^-$. When applied appropriately, the derived ratio from this formula will unmask the presence of another acid–base disorder that is superimposed on the primary acid–base disturbance.

In summary, the physiologic method follows $[H^+]$, pH, HCO_3^-/CO_2 buffer system, AG, and $\triangle AG/\triangle HCO_3^-$ with secondary physiologic response to explain both primary metabolic and respiratory as well as mixed acid–base disorders. However, this method has been criticized by many investigators. Some of the critic in terms of merits and drawbacks is presented below.

Merits

1. It is widely used because it is simple and easy to follow at bedside
2. The AG is easy to calculate, and the corrected AG is useful in elucidating the cause of metabolic acidosis
3. It is easy to evaluate the mixed acid–base disorder and its etiology

Drawbacks

1. The method is descriptive rather than mechanistic in nature
2. No linear relationship exists between pH and $[H^+]$ throughout the pH scale (see Table 1.1). For example, the decrease in pH from 7.40 to 7.20 is associated with linear increase in $[H^+]$ from 40 to 63 nmol/L, whereas a drop from 7.00 to 6.80 is associated with nonlinear increase from 100 to 159 nmol/L. This suggests that changes in pH are not consistent with changes in $[H^+]$
3. The Henderson–Hasselbalch equation suggests only HCO_3^-/CO_2 buffer system and not the other buffer systems, although this equation considers HCO_3^-/CO_2 buffer is in equilibrium with other buffer systems (isohydric principle).
4. The Henderson–Hasselbalch equation does not include all concentrations of anions and cations in the evaluation of acid–base balance
5. Although pCO_2 and HCO_3^- are interdependent, the physiologic method assumes HCO_3^- behaves like an independent variable, and its concentration determines the metabolic component of acid–base disorder
6. HCO_3^- is not always a representative of metabolic acidosis, because concentration is high not only in metabolic alkalosis but also high in chronic respiratory acidosis. Similarly $[HCO_3^-]$ is low both in metabolic acidosis and respiratory alkalosis. Thus, HCO_3^- alone is not the only determinant of metabolic acid–base

disorder because its concentration is affected both by pCO_2 (a respiratory component) and pH or $[H^+]$ (a metabolic component)
7. Uncorrected AG may lead to incorrect analysis of metabolic acidosis

Base Excess Method

It is well established that pCO_2 is the determinant of respiratory acid–base disorder. Since HCO_3^- is dependent on pCO_2, several investigators tried to develop an independent marker to identify metabolic (nonrespiratory) acid–base disorder independent of pCO_2. Some of the terms that were proposed to express the metabolic component of the acid–base disorder were (1) buffer base, (2) standard HCO_3^-, and (3) base excess. We will discuss briefly these three terms.

Historically, the concept of base excess originated from the work of Singer and Hastings in 1948 [4], who introduced the term whole-blood *buffer base* as a measure of metabolic acid–base disturbance independent of pCO_2 and HCO_3^-. They defined buffer base as the sum of fixed cations (or strong bases) minus the sum of fixed anions (strong acids). A fixed ion is an ion that is unable to bind or give off an H^+. The important fixed cations in plasma are Na^+ and K^+ except H^+. The important fixed anion in plasma is Cl^-, and nonfixed anions are HCO_3^-, albumin, hemoglobin, and phosphate. These nonfixed anions are considered weak acids or buffer acids, as they bind H^+. Based on the above information, buffer base is simply defined as the sum of plasma HCO_3^- and nonfixed buffer ions such as albumin, hemoglobin, and phosphate.

As buffer base is defined as the sum of plasma HCO_3^- and nonfixed buffer ions such as albumin, hemoglobin, and phosphate, it can be calculated in *plasma* at pH of 7.40 and pCO_2 of 40 mmHg, as follows:

$$\text{Buffer base} = 24\left(HCO_3^-\right) + 12.3\left(\text{albumin}\right) + 2.7\left(\text{phosphate}\right) = 39\,\text{mEq/L}$$

Base buffer in whole blood is 48 mEq/L because of hemoglobin (15 g/dL = 9 mEq). Accordingly, a decrease in buffer base indicates metabolic acidosis, and an increase is suggestive of metabolic alkalosis.

Although measurement of buffer base was not easy in 1948, Singer and Hastings constructed a nomogram from which they derived the value of buffer base. Singer and Hastings did not recognize that buffer base, as mentioned above, does not change with respiratory disturbance. However, in the whole body or in vivo, the buffer base does not remain constant. Also, buffer base changes with changes in albumin and hemoglobin concentrations.

In subsequent years, other investigators, particularly, Siggaard-Andersen, Engel as well as Astrup [5–8], introduced the term *base excess* as a measure to quantify the metabolic (nonrespiratory) component of an acid–base disorder. To determine the base excess, Siggaard-Andersen and colleagues conducted in vitro experiments that

equilibrated blood at pCO_2 of 40 mmHg and at 37 °C to avoid any respiratory interference. They then quantified the amount of either strong acid (HCl) or strong base (NaOH) required to return 1 L of whole blood to a pH of 7.40. This quantity of acid or base is called the base excess, which is negative when NaOH was used (acidosis) or positive when HCl was used (alkalosis). Base excess is, thus, defined as the amount of base or acid required to titrate in vitro 1 L of whole blood to a pH of 7.40 at pCO_2 of 40 mmHg and a temperature of 37 °C. These equilibration studies were performed with whole blood with the hemoglobin concentration of approximately 14–15 g/dL. As hemoglobin is the most important nonbicarbonate buffer, changes in hemoglobin will influence not only buffer base but also base excess. Since blood was equilibrated with pCO_2, base excess is not influenced by changes with respiration or pCO_2.

In vitro evaluation of base excess may not be applicable to in vivo or whole organism, since CO_2 equilibration in vivo occurs not only in blood (intravascular) but in interstitial compartment (extravascular) as well. Also, hemoglobin concentration is not the same in blood and interstitium because of different water content in both compartments. Interstitium has more water content than intravascular compartment, and thus hemoglobin concentration is much lower in the interstitial compartment. This will cause changes in base excess. To overcome this, Siggaard-Andersen modified the original equation of base excess and introduced the term *standard base excess* as a measure of metabolic component of an acid–base disorder. This standard base excess was derived from equilibration with hemoglobin concentration of 5 g/dL, which is the concentration in the interstitium. Initially, a nomogram was constructed to read the standard base excess value, but currently blood gas analyzers automatically measure standard base excess as base excess.

Base excess (mEq/L) is usually expressed as positive (+) or negative (−). Positive base excess means an excess of base or lack of acid, and a negative base excess indicates excess of acid or lack of base. Negative base excess is also called base deficit, which is expressed numerically as 5 or −5. Also, base deficit is expressed as base excess −5. Thus, base deficit and base excess are used interchangeably. Normal base excess values range from −3 to +3. Therefore, base excess of −5 indicates metabolic acidosis, whereas +5 indicates metabolic alkalosis.

Base excess values are frequently used in critically ill patients to analyze acid–base disturbance [9]. For example, the pH indicates either acidosis or alkalosis, pCO_2 indicates the respiratory component, and base excess implies the metabolic component. Thus, the intensivists and anesthesiologists will have a quick analysis of an acid–base disturbance at bedside to make therapeutic decisions.

Base excess seems to have a prognostic value in critically ill patients [9]. Studies in trauma, burn, and other ill patients have shown that negative base excess (−6 mEq/L) carried high morbidity and mortality. However, no consistent correlation was found between base excess and other metabolic parameters such as lactate, HCO_3^-, or uncorrected or corrected AG.

Similar to physiologic approach, base excess method has some merits and drawbacks.

Merits

1. Easy to apply at the bedside
2. As mentioned above, base excess is a prognostic indicator in trauma and burn patients
3. Base excess can be used to calculate the amount of $NaHCO_3$ needed to correct the base deficit to improve pH, as follows:

   Patient's weight (kg)
   HCO_3^- space (usually 30–40% of body weight)
   Base deficit (e.g., −6 mEq/L)
   Example: Weight = 70 kg
   HCO_3^- space = 40%
   Base deficit = 6
   Amount of $NaHCO_3$ needed = $70 \times 0.4 \times 6 = 168$ mEq

Drawbacks

1. Base excess measurements are variable from machine to machine. Not only intermachine variability but also intramachine variability is rather common. This variability may lead to incorrect diagnosis and raises the question of clinical validity of base excess. A variability in base excess of approximately 3.7 mEq/L has been reported when measured with different modern blood gas analyzers
2. Base excess can be altered by (1) dilution of plasma, (2) changes in Cl^-, and (3) changes in albumin and unmeasured anions
3. Base excess is calculated from the arterial blood sample and may not be useful with venous blood samples
4. The negative (e.g., −4) or positive (e.g., +4) base excess does not necessarily mean that metabolic acidosis or alkalosis is present. For example, in chronic respiratory acidosis, the base excess is positive due to compensatory increase in $[HCO_3^-]$ in the absence of metabolic alkalosis and negative in chronic respiratory alkalosis due to a decrease in $[HCO_3^-]$ in the absence of metabolic acidosis. In acute respiratory acidosis, the base excess is normal, but pCO_2 is high
5. In mixed acid–base disorders, base excess may lead to erroneous diagnosis. For example, the base excess in a patient with chronic respiratory acidosis is positive. If this patient develops acute metabolic acidosis (lactic acidosis due to sepsis), the base excess decreases without much change in pCO_2, suggesting that the patient has acute respiratory acidosis rather than metabolic acidosis that is superimposed on chronic respiratory acidosis. Thus, the real diagnosis of acid–base disturbance is missed. The above example also suggests that base excess cannot determine the cause of metabolic acidosis

Analysis of an Acid–Base Disorder Using Physiologic and Base Excess Methods

With the above discussion, let us analyze one of the hypothetical cases of Schwartz and Relman [10] and evaluate whether the physiologic or base excess method is appropriate or not.

Case	Normal
pH = 7.32	pH = 7.40
pCO_2 = 80 mmHg	pCO_2 = 40 mmHg
HCO_3^- = 40 mEq/L	HCO_3^- = 24 mEq/L
Standard HCO_3^- = 32 mEq/L	Standard HCO_3^- = 23 mEq/L
Base excess = 11 mEq/L	Base excess = −3 to +3 mEq/L

Physiologic Method

The pH of 7.32 indicates either metabolic acidosis or respiratory acidosis. In metabolic acidosis, however, both pCO_2 and HCO_3^- are lower than normal values, and in respiratory acidosis both are above normal values. The observed pCO_2 in the case is 80 mmHg, which indicates either acute or chronic respiratory acidosis. Applying the physiologic rules of thumb principles for compensation, the change in HCO_3^- is as follows (Table 3.1):

Acute respiratory acidosis: For each mmHg increase in pCO_2 above normal value, HCO_3^- increases by 0.1 mEq/L. Using this rule, the expected HCO_3^- is 4 mEq/L (80–40 = 40 × 0.1 = 4)

Chronic respiratory acidosis: For each mmHg increase in pCO_2, HCO_3^- above normal value increases by 0.4 mEq/L. Using this rule, the expected HCO_3^- is 16 mEq/L (80–40 = 40 × 0.4 = 16). The observed HCO_3^- was 40 mEq/L, and the acid–base disorder in this patient is a primary chronic respiratory acidosis. No other acid–base disorder is superimposed on this chronic respiratory acidosis.

Base Excess Method

Base excess method introduces, as discussed before, standard HCO_3^- and base excess as indicators of metabolic component of acid–base disorder. In this patient, both are elevated. This suggests that metabolic alkalosis is superimposed on respiratory acidosis. Thus, the patient has a mixed acid–base disorder, which would lead to incorrect therapeutic decision.

Based on the above discussion, the physiologic method appears to be simple and appropriate compared to the base excess method.

The Transatlantic Acid–Base Debate

The concept of base excess was introduced by Siggaard-Andersen and colleagues [5–8] from Copenhagen. Schwartz and Relman [10] from Boston challenged this concept, as these investigators proved that actual [HCO_3^-] in blood determines the metabolic component of the acid–base disorder. These investigators provided several examples of acid–base disorders and proved that calculation of base excess can lead to misdiagnosis, which will lead to incorrect therapeutic decisions. Also, they pointed out the disadvantages of base excess, as mentioned above. Bunker [11] wrote an editorial of the controversy between the Danish and American scientists and called it "the great transatlantic acid–base debate" and provided evidence in support of the argument by the Boston group. With the introduction of "rules of thumb" (secondary physiologic response to primary acid–base disorder) by Schwartz and Relman (see Table 1.3 in Chap. 1), the physiologic approach remained the most popular method of teaching acid–base disorders by the nephrologists, renal physiologists, and internists. However, blood gas machines report both calculated HCO_3^- and base excess in the same report, thus satisfying both schools of thought.

Physicochemical Method

In the late 1970s and early 1980s, a Canadian-born American physical chemistry and mathematics professor, Peter Stewart, proposed an alternative approach to acid–base disorders [12–14]. He challenged the traditional bicarbonate-based approach because HCO_3^- alone does not determine metabolic acid–base disorder. According to Stewart, each body fluid compartment or aqueous solution such as plasma should have in common both "strong" and "weak" electrolytes as cations and anions, and these electrolytes determine the status of acid–base balance in health and disease. Strong electrolytes are the ones that are fully dissociated, and weak electrolytes are those that are partially dissociated in an aqueous solution (see Table 3.2). Therefore, these electrolytes in each body fluid compartment must operate strictly under three physicochemical principles:

Table 3.2 Strong and weak ions

Strong ions	Weak ions
Na^+	HCO_3^-
K^+	Albumin
Ca^{2+}	HPO_3^{2-}
Mg^{2+}	
Cl^-	
SO_4^{2-}	
Lactate	

1. Electroneutrality: This principle means that the sum of all cations must equal the sum of all anions. Therefore, the net charge in a compartment is zero
2. Conservation of mass: This means that the amount of a substance in solution is constant unless added or removed. The relevance is that the total concentration of an incompletely dissociated substance in a solution is equal to the concentrations of both dissociated and undissociated forms
3. Law of mass action: This suggests that the dissociation equilibriums of all incompletely dissociated substances must be met at all times

Based on these physicochemical principles for acid–base analysis, Stewart derived six equations:

1. Water dissociation equilibrium: $[H^+] \times [OH-] = K_W$
2. Weak acid dissociation equilibrium: $[H^+] \times [A^-] = K_A \times [HA]$
3. Conservation of mass for weak acid equilibrium: $[HA] + [A^-] = [A_{TOT}]$
4. Bicarbonate ion formation equilibration: $[H^+] \times [HCO_3^-] = K_C \times pCO_2$
5. Carbonate (CO_3^{2-}) ion formation equilibrium: $[H^+] \times [CO_3^{2-}] = K_3 \times [HCO_3^-]$
6. Electrical neutrality equilibrium: $[SID] + [H^+] = [HCO_3^-] + [A^-] + [CO_3^{2-}] + [OH^-]$

where K_W, K_C, and K_3 are dissociation constants, HA weak acid, A^- conjugate base, $[A_{TOT}]$ total concentration of nonvolatile weak acids (proteins and phosphate), and SID strong ion difference.

Stewart starts with plasma water. According to him, changes in plasma $[H^+]$ are related to water dissociation, which provides an infinite source of H^+ and OH^-. Thus, changes in $[H^+]$ should be viewed as changes in water dissociation rather than addition or removal of H^+ from plasma. A solution is considered neutral if the concentration of H^+ is equal to the concentration of OH^-. Pure water is thus considered neutral. An acid is the one that has more H^+ than OH^-, and a base has less H^+ than OH^-. These definitions of acid and base are different than those of BrØnsted–Lowry's definitions. Stewart also differs from the traditional approach by proposing that the source of H^+ is water and not carbonic acid (Eq. 3.3).

Following these definitions, Stewart proposed that changes in $[H^+]$ and consequently in pH are influenced by three independent variables. Independent variables are defined as those that influence the system (plasma) but are not influenced by the system. These independent variables are:

1. pCO_2
2. Strong ion difference (SID)
3. Total concentration of weak acids $[A_{TOT}]$

pCO_2

pCO_2, as an independent variable of $[H^+]$, is treated similarly by all three methods. Tissues produce CO_2, which diffuses easily between body compartments. Because of this easy diffusibility and rapid dissociation of H_2CO_3 to H^+ and HCO_3^-, $[H^+]$ can

change easily. For example, when pCO_2 rises, physicochemical principles dictate that $[H^+]$ must rise. Similarly, when pCO_2 decreases, $[H^+]$ must decrease. Thus, pCO_2 can influence $[H^+]$.

Strong Ion Difference (SID) As defined above, strong electrolytes or ions dissociate completely, and weak ions dissociate partially in aqueous solutions. SID is defined as the difference between the total concentrations of strong cations and the total concentration of strong anions (see Table 3.2). In other words, SID in a healthy individual (pH = 7.40) is:

$$\text{SID} = \left[\text{Strong cations}\right] = \left[\text{Strong anions}\right]$$

Since all strong ions are not measured routinely, SID is not measured directly, but it can be calculated as follows:

$$\text{SID} = \left(\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+}\right) \quad \left(\text{Cl}^-\right) + \left(\text{Lactate}^-\right) \tag{3.4}$$

In plasma, Na^+ and Cl^- are the major cation and anion, respectively. If the concentrations of these two strong ions are available, SID can be calculated by the following formula:

$$\text{SID} = \text{Na}^+ - \text{Cl}^- = 40 \text{ mEq/L} \left(140 - 100 = 40 \text{ mEq/L}\right) \tag{3.5}$$

SID values vary from 39 to 42 mEq/L, depending on the plasma concentrations of Na^+ and Cl^-. Because $[Na^+]$ is greater than $[Cl^-]$, SID is always positive. In healthy subjects, this positive charge is balanced by the negative charge present on HCO_3^-, albumin, and phosphate to maintain electroneutrality. Thus, SID is zero in a healthy individual because of electroneutrality. Changes in SID result in changes in metabolic acid–base disturbance. When SID is <39 mEq/L due to a decrease in cations or an increase in anions, metabolic acidosis develops. On the other hand, if SID is >42 mEq/L, it indicates metabolic alkalosis.

The SID, calculated as in Eq. 3.4, is called apparent SID (SID_a). As shown in Eq. 3.4, the SID_a does not include other anions such as HCO_3^-, proteins, and phosphate. When these anions are included in the calculation, the SID is called effective SID (SID_e). SID_e is similar or equivalent to buffer base, as proposed by Singer and Hastings [4]. The difference between SID_a and SID_e is called strong ion gap (SIG), which represents some of the unmeasured anions such as ketones, SO_4^{2-}, and urate. Normal SIG values range from 0 to 2 mEq/L. SIG is similar to AG, representing unmeasured anions. A close correlation exists between SIG and AG, in particular with corrected AG for hypoalbuminemia. The difference between SIG and AG is that SIG is not affected by hypoalbuminemia or dehydration. When SIG is positive (>2 mEq/L), it suggests the presence of more anions than cations with resultant metabolic acidosis such as diabetic ketoacidosis. Stewart's approach was favorably analyzed by several investigators [15–19].

At bedside, SID_e is difficult to calculate. Fencl and associates [20] introduced a simplified version of SID_e, as follows:

$$SID_e = \left[HCO_3^-\right] + 0.28 \times \left[\text{Albuming / L}\right] + 1.8 \times \left[\text{phosphate}\left(\text{mmol / L}\right)\right] \quad (3.6)$$

where 0.28 and 1.8 are negative charges (in mEq/L) displayed by 1 g of albumin and 1 mmol of phosphate, respectively, at plasma pH of 7.40. If the units of phosphate are in mg/dL, the factor is 0.6. To convert phosphate into mmol/L, multiply mg/dL by 0.32.

Example

HCO_3^- = 24 mEq/L
Albumin = 44 g/L
Phosphate = 4.5 mg/dL

$$SID_e = 24 + 12.3\left(44 \times 0.28\right) + 2.7\left(4.5 \times 0.6\right) = 39\,\text{mEq / L} \quad (3.7)$$

Total Concentration of Weak Acids [A_{TOT}]

As stated, weak acids are not dissociated completely in aqueous solutions. A_{TOT} consists of proteins (mostly albumin) and phosphate. When [A_{TOT}] increases, [H^+] increases, and when [A_{TOT}] decreases, [H^+] also decreases. For example, hyperphosphatemia is associated with metabolic acidosis, whereas hypoalbuminemia is associated with metabolic alkalosis. Hypoalbuminemic metabolic alkalosis is not a clinical condition that warrants treatment. Similarly hyperalbuminemia results in metabolic acidosis, a condition not clinically significant.

It is clear from the above discussion that only the three independent variables determine the [H^+] or pH, and not the HCO_3^- by itself. Therefore, H^+ and HCO_3^- are considered dependent variables.

Stewart's Classification of Acid–Base Disorders

Based on the variations of three independent variables, the acid–base disorders were classified into respiratory and metabolic components, as shown in Table 3.3 (adapted from Ref. [20]).

It is evident from Table 3.3 that metabolic acidosis or metabolic alkalosis is caused by changes either in SID or A_{TOT} or both. For example, a decrease in SID (more anions than cations) represents acidosis, and an increase in SID (more cations than anions) suggests alkalosis. When SID decreases, water dissociation is enhanced to generate more H^+ so that the pH of the body fluid decreases. In cases of high SID

Table 3.3 Acid–base disorders

Independent variable	Acidosis	Alkalosis
Respiratory		
pCO_2	↑pCO_2	↓pCO_2
Metabolic		
SID		
Water excess	↓SID, [↓Na^+]	
Water deficit		↑SID [↑Na^+]
Hyperchloremia	↓SID	
Hypochloremia		↑SID
Lactic or ketoacidosis	↓SID ↑SIG	
A_{TOT}		
Hyperalbuminemia	Yes	
Hypoalbuminemia		Yes
Hyperphosphatemia	Yes	
Hypophosphatemia		Yes

values, water dissociation decreases with resultant decrease in H^+ production and an increase in pH. The following examples illustrate the role of SID in metabolic acid–base disturbances.

Example 1 Hypercholemic metabolic acidosis due to saline infusion

Normal saline has a SID of zero because it contains 154 mEq of Na^+ and 154 mEq of Cl^-. When several liters of normal saline are infused to correct volume depletion, hyperchloremic metabolic acidosis develops. This is due to the high Cl^- concentration of saline compared to normal plasma Cl^- concentration (100 mEq/L). Although both plasma concentrations of Na^+ and Cl^- increase, the increase is more in Cl^- relative to Na^+ [21]. This causes a reduction in SID, and H^+ production increases with increased water dissociation to maintain electroneutrality. Thus, hyperchloremic metabolic acidosis due to normal saline results from decreased SID rather than from low [HCO_3^-] due to dilution.

Example 2 Dilutional acidosis due to water excess

5% dextrose in water (D5W) has no strong ions, and its SID is zero. When large volumes of D5W are given to a patient with mild impairment in renal function, dilution of many strong ions occurs. However, reduction in [Na^+] is more than reduction in [Cl^-]. In this situation, hyponatremia and relative hyperchloremia develop, causing SID to decrease. The result is the development of dilutional acidosis, which is not related simply to a decrease in [HCO_3^-].

Example 3 Contraction alkalosis

In contrast to dilutional acidosis, contraction alkalosis from loss of body water with more increase in plasma [Na^+] than [Cl^-] causes SID to increase and the development of contraction alkalosis.

Example 4 Metabolic alkalosis due to vomiting or nasogastric suction

With vomiting or nasogastric suction, both H^+ and Cl^- are lost, and metabolic alkalosis develops. Because of loss of Cl^-, SID increases. Decrease in Cl^- causes less dissociation of water with low H^+ production. Hypochloremia and low H^+ production raise blood pH and cause metabolic alkalosis. Thus, metabolic alkalosis due to loss of HCl from vomiting is not related to loss of H^+ because it can generate from water dissociation but with decreased quantity.

In summary, Stewart's method is based on the principles of electroneutrality, law of mass conservation, and law of mass action or dissociation constants of electrolytes. Water is the source of H^+, and its plasma concentration or pH is dependent on three independent variables, namely, SID, pCO_2, and total weak acids (A_{TOT}). Thus, changes in these independent variables result in changes in $[H^+]$ or pH. This indicates that H^+ and HCO_3^- are dependent variables. Unlike traditional approach, Stewart's approach is more mechanistic in complex metabolic acid–base disorders. However, there are several controversies regarding Stewart's methodology, and merits and drawbacks of this approach are described below:

Merits

1. As mentioned above, the method is mechanistic, as it provides the cause of a metabolic acid–base disorder
2. SIG is superior to AG in detecting unmeasured anions such as ketones
3. HCO_3^- is not the determinant of pH, as $[HCO_3^-]$ may change not only in metabolic acid–base disorders but also in respiratory acid–base disorders
4. H^+ comes from water dissociation to maintain electroneutrality
5. Changes in SID and A_{TOT} determine metabolic acid–base disorders

Drawbacks

1. Stewart's approach is difficult to apply at bedside because of its complexity. Despite the availability of calculators and computers, calculations of SID and A_{TOT} require time for therapeutic decisions
2. Production of H^+ from water dissociation and its increase due to reduced SID and decrease due to increased SID to maintain electroneutrality in vivo lacks experimental evidence
3. According to Stewart, the three independent variables are not modifiable by the system (referring to plasma only). Since plasma is in equilibrium with other systems or compartments such as interstitium, red blood cells, etc., Stewart's method does not explain whether or not these variables are modifiable in these body fluid compartments

4. The clinical significance of hypoalbuminemia- or hypophosphatemia-induced metabolic alkalosis is not explained unless the alkalemia reduces the severity of metabolic acidosis that is frequently present in critically ill septic patient.
5. As shown in Table 3.3, changes in SID and A_{TOT} are the result rather than the cause of metabolic acid–base disorders. The are no in vivo experimental data to dispute this argument.

Analysis of an Acid–Base Disorder Using Physiologic and Physicochemical Methods

In order to appreciate both physiologic and physicochemical approaches, one can use a case from the literature and analyze it by both methods. We will evaluate the case of Corey [22] and analyze it logically without any bias. "A critically ill patient with septic shock and multiple organ failure. The management consisted of cardiopressors, mechanical ventilation, antibiotics, and large volume of normal saline." Labs:

Labs	ABG
Measured values	pH = 7.10
Na^+ = 130 mEq/L	pCO_2 = 30 mm hg
K^+ = 3.0 mEq/L	Base excess = −15 mEq/L
Cl^- = 111 mEq/L	
HCO_3^- = 9.25 mEq/L	
Albumin = 1.5 g/dL	
Phosphate = 2.0 mg/dL	
Calculated values (mEq/L)	
Anion gap (AG; uncorrected) = 9.75[a]	
AG (corrected) = 17.15	
$\triangle$AG = 17.5–10 = 7.5	
$\triangle HCO_3^-$ = 24–9.25 = 14.75	
SID_a = 22 (normal = 40)[b]	
SID_e = 14 (normal = 40)	
SIG = 8 (normal = 0)	

[a]Normal AG = 10 mEq/L
[b]See Table 3.4 for calculations

Physiologic Approach

1. Dominant acid–base disorder: High AG metabolic acidosis. Negative base excess also supports this diagnosis
2. Respiratory response: Using the rules of thumb for metabolic acidosis, the expected pCO_2 should be 22 mm Hg; instead, the patient's pCO_2 is 30 mm Hg.

Table 3.4 Summary of formulas used in the calculation of standard bicarbonate excess and other Stewart's quantitative terms

Term	Calculation
Strong ion difference (SID)	1. $(Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + lactate^-)$ 2. $[HCO_3^-] + 0.28 \times$ [albumin g/L] $+ 1.8 \times$ [phosphate mmol/L] 3. $Na^+ - Cl^-$
Apparent SID (SID_a)	$(Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + lactate^-)$
Effective SID (SID_e)	$(2.46 \times 10^{-8} \times pCO_2/10^{-pH}) +$ (albumin g/dL) $\times (0.123 \times pH - 0.631)$ + (phosphate mmol/L) $\times (pH - 0.469)$
Strong ion gap (SIG)	$SID_a - SID_e$
Standard bicarbonate excess (SBE)	$0.9287 \times HCO_3^- - 24.4 + 14.83 \times (pH - 7.4)$
Anion gap (AG)	$Na^+ - (Cl^- + HCO_3^-)$
Corrected anion gap (AG_C)	For each gram decrease from normal albumin level of 4.4 g/dL, add 2.5 mEq/L to uncorrected AG

Thus, the patient has superimposed respiratory acidosis due to incomplete respiratory secondary response (compensation)

3. Hyperchloremic metabolic acidosis: Cl^- is high due to infusion of normal saline. The $\triangle$AG of 7.5 is expected to decrease HCO_3^- from 24 to 16.5 mEq/L. (24–7.5 = 16.5 mEq/L). Instead, the patient's HCO_3^- is 9.25 mEq/L, and the difference between the expected and observed decrease in HCO_3^- (16.5–9.25 = 7.25 mEq/L) is due to an increase in Cl^- concentration to maintain electroneutrality. The $\triangle AG/\triangle HCO_3^-$ (7.5/14.75 = 0.5) is suggestive of normal saline infusion. In the absence of saline infusion, diarrhea or renal tubular acidosis can reduce HCO_3^- to 9.25 mEq/L

The final analysis of this acid–base disorder is high AG metabolic acidosis, respiratory acidosis, and hyperchloremic acidosis. High AG is due to lactic acid from hypoperfusion and hypotension, ketoacids probably from starvation (no mention of blood or urine ketones), and acute kidney injury (multiorgan failure). Thus, the physiologic approach explains all the mechanisms involved in this triple acid–base disorder [23]. Besides treating sepsis, the appropriate fluid is Ringer's lactate as this fluid may correct electrolytes and improve metabolic acidosis. Frequent monitoring of lactate is necessary because of lactate in Ringer's solution. Continuation of normal saline worsens metabolic acidosis. Ventilatory management improves respiratory acidosis.

Physicochemical Approach

1. Hyperchloremia causes low SID. Therefore, the patient has hyperchloremic metabolic acidosis due to saline infusion
2. High SIG refers to accumulation of unmeasured strong anions such as lactate, ketones, sulfates, and urate. In this patient, lactate seems to be the major strong anion because of sepsis. Thus, the patient has lactic acidosis

3. Respiratory acidosis is present due to inadequate respiratory compensation of pCO_2 (pCO_2 is >22 mm Hg)
4. Hypoalbuminemic alkalosis

The final analysis of this acid–base disorder is hyperchloremic metabolic acidosis, lactic acidosis, respiratory acidosis, and hypoalbuminemic metabolic alkalosis. Management of acid–base disorder is the same, as described above; however, treatment of alkalemia due to hypoalbuminemia is not necessary. Actually hypoalbuminemia is protective of raising pH in this patient.

Comment

As discussed above, both approaches provided the same final diagnosis and mechanisms or causes of the acid–base disorder in this critically ill patient described by Corey [22]. However, Stewart's approach requires calculation of SID and SIG, which is time-consuming. In critical care units, serum lactate, ketones (both serum and urine), creatinine, and albumin are routinely measured in a patient with severe metabolic acidosis due to sepsis or multiorgan failure. Based on these values, secondary physiologic (compensatory) response to the main acid–base disorder and the corrected AG, the cause for any complex acid–base disturbance can be delineated accurately with the physiologic approach without spending time on calculations of SID and SIG. Base excess is measured by the blood gas analyzer, and it does not require any calculation. In the author's opinion, both methods provide similar mechanisms for any complex acid–base disturbance, but the physiologic approach is easy to apply at the bedside.

A number of reviews compared both physiologic and physicochemical methods in the evaluation of acid–base disturbances and concluded that both methods are similarly mechanistic [24–27]. As stated above, the physicochemical method takes more time than the physiologic method in arriving at similar conclusions.

References

1. Po HN, Senozan NM. The Henderson-Hasselbalch equation: its history and limitations. J Chem Ed. 2001;78:1499–503.
2. Astrup P, Severinghaus JW. The history of blood gases, acids and bases. Munkgaard: Copenhagen; 1986.
3. Kurtz I, Kraut J, Ornekian O, Nguyen M. Acid-base analysis: a critique of the Stewart and bicarbonate-centered approaches. Am J Physiol Renal Physiol. 2008;294:F1009–31.
4. Singer RB, Hastings B. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine (Baltimore). 1948;27:223–42.
5. Siggaard-Andersen O. The van Slyke equation. Scan J Clin Lab Invest. 1977;37(suppl):15–20.
6. Siggaard-Andersen O. The acid-base status of the blood. 4th ed. Baltimore: Williams & Wilkins; 1974.

7. Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anaesthesiol Scand. 1995;107(Suppl):123–8.
8. Astrup P, JØrgensen K, Siggaard-Andersen O, Engel K. Acid-base metabolism. A new approach. Lancet. 1960;1:1035–9.
9. Juern J, Khatri V, Weigelt J. Base excess: a review. J Trauma Acute Care Surg. 2012;73:27–32.
10. Schwartz WB, Relman AS. A critique of the parameters used in the equation of acid-base disorders. "Whole-blood buffer base" and "standard bicarbonate" compared with blood pH and plasma bicarbonate concentration. N Engl J Med. 1963;268:1382–8.
11. Bunker JP. The great trans-atlantic acid-base debate. Anesthesiology. 1965;26:591–4.
12. Stewart PA. Independent and dependent variables of acid-base control. Resp Physiol. 1978;33:9–26.
13. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol. 1983;61:1444–61.
14. Kellum JA, Elbers PWG, editors. Stewart's textbook of acid-base. 2nd ed. Amsterdam: PW Elbers and ACIDBASE.org; 2009.
15. Fencl V, Rossing TH. Acid-base disorders in critical care medicine. Ann Rev Med. 1989;40:17–29.
16. Constable PD. Clinical assessment of acid-base status: comparison of the Henderson-Hasselbalch and strong ion approaches. Vet Clin Pathol. 2000;29:115–28.
17. Kellum JA. Disorders of acid-base balance. Crit Care Med. 2007;35:2630–6.
18. Morgan TJ. The Stewart approach-one clinician's perspective. Clin Biochem Rev. 2009;30:42–54.
19. Story DA. Stewart acid-base: a simplified bedside approach. Anesth Analg. 2016;123:511–5.
20. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbance in critically ill patients. Am J Respir Crit Care Med. 2000;162:2246–51.
21. Story DA. Intravenous fluid administration and controversies in acid-base. Crit Care Resuscit. 1999;1:151–6.
22. Corey HE. Stewart and beyond: new models of acid-base balance. Kidney Int. 2003;64:777–87.
23. Emmett M. Clinical acid-base disorders: traditional versus "new" analytical models. Kidney Int. 2004;65:1112. (letter to the editor)
24. Adroguė HJ, Gennari FJ, Galla JH, Madias NE. Assessing acid-base disorders. Kidney Int. 2009;76:1239–47.
25. Rastegar A. Clinical utility of Stewart's method in diagnosis and management of acid-base disorders. Clin J Am Soc Nephrol. 2009;4:1267–74.
26. Seifter JL. Integration of acid-base and electrolyte disorders. N Engl J Med. 2014;371:1821–31.
27. Masevicius FD, Dubin A. Has Stewart's approach improved our ability to diagnose acid-base disorders in critically ill patients? World J Crit Care Med. 2015;4:60–70.

Chapter 4
Acid–Base Disorders: General Considerations and Evaluation

The assessment of an acid–base disorder by three methods was discussed in Chap. 3. In this and other chapters, we follow the physiologic method for evaluation of an acid–base disorder. In Chap. 1, we stated that a change in plasma [HCO_3^-] results in a metabolic acid–base disturbance, whereas a change in arterial pCO_2 results in a respiratory acid–base disorder. Clinically, four primary acid–base disorders can be recognized: (1) *metabolic acidosis*, (2) *metabolic alkalosis*, (3) *respiratory acidosis*, and (4) *respiratory alkalosis*. Values for an arterial blood gas (ABG) for each primary acid–base disorder are shown in Table 4.1. Table 4.2 shows the terminology that is useful to a clinician in the analysis of an acid–base disorder.

Concepts in the Evaluation of an ABG

Three concepts (two of them not defined in Table 4.2) that help you evaluate the acid–base disorders are the *Henderson equation*, the *anion gap*, and the *secondary physiologic response* (*compensation*).

Table 4.1 Primary acid–base disturbances and their secondary response

Acid–base disorder	pH	Primary change	Secondary change	Mechanism of secondary change
Metabolic acidosis	<7.40	↓ HCO_3^-	↓ pCO_2	Hyperventilation
Metabolic alkalosis	>7.40	↑ HCO_3^-	↑ pCO_2	Hypoventilation
Respiratory acidosis	<7.40	↑ pCO_2	↑ HCO_3^-	↑ HCO_3^- reabsorption
Respiratory alkalosis	>7.40	↓ pCO_2	↓ HCO_3^-	↓ HCO_3^- reabsorption

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_4

Table 4.2 Acid–base terminology

Acidemia: an increase in blood [H^+]
Alkalemia: a decrease in blood [H^+]
Acidosis: a pathophysiologic process that tends to acidify body fluids
Alkalosis: a pathophysiologic process that tends to alkalinize body fluids
Arterial blood gas (ABG): includes pH, pCO_2, and calculated serum [HCO_3^-]
Normocapnia: normal arterial pCO_2 (40 mmHg)
Hypocapnia: a decrease in arterial pCO_2
Hypercapnia: an increase in arterial pCO_2
Normobicarbonatemia: normal serum [HCO_3^-] (24 mEq/L)
Hypobicarbonatemia: a decrease in serum [HCO_3^-]
Hyperbicarbonatemia: an increase in serum [HCO_3^-]
Primary change: an abnormality in either the serum [HCO_3^-] or arterial pCO_2 resulting from a primary change in body function/metabolism or additions to or losses from body fluids
Secondary change: a compensatory (secondary) response that acts to minimize changes in pH produced by the primary disorder. It is also called compensation
Simple acid–base disorder: presence of one primary disorder with appropriate secondary response
Mixed acid–base disorder: simultaneous occurrence of two or more primary disorders

Henderson Equation

In clinical practice, the Henderson–Hasselbalch equation is a rather cumbersome way to calculate the pH using logarithms. The same information can be obtained by using the *Henderson equation*, which relates [H^+] to pH. This equation, which calculates [H^+], is expressed as:

$$H^+\left(\text{nmol/L}\right) = 24 \times \frac{pCO_2}{\left[HCO_3^-\right]}$$

As an example of how this equation can be used, consider the following ABG values:

pH = 7.40
pCO_2 = 40 mmHg
HCO_3^- = 24 mEq/L

$$H^+\left(\text{nmol/L}\right) = 24 \times \frac{40}{24} = 40$$

This [H^+] of 40 corresponds to the pH of 7.40. The Henderson equation is thus used clinically to check the validity of pH obtained from the clinical laboratory.

Remember the following approximate [H^+] to clinically relevant pH values:

pH 7.50 = 30
pH 7.40 = 40

pH 7.30 = 50
pH 7.20 = 60
pH 7.10 = 80
pH 7.00 = 100

The Henderson equation can also be used to calculate the [HCO_3^-]:

$$\left[HCO_3^- \right] \left(mEq/L \right) = 24 \times \frac{pCO_2}{\left[H^+ \right]}$$

The HCO_3^- that is reported in the ABG slip is the calculated one from the above equation, and this value is 1–2 mEq/L less than the measured serum HCO_3^-, which is usually called total or TCO_2. TCO_2 includes HCO_3^-, carbonic acid, and dissolved CO_2. For this reason, the measured HCO_3^- is 1–2 mEq higher than the calculated HCO_3^-. In the evaluation of ABG, if there is large difference between the measured and calculated HCO_3^-, the ABG and electrolytes should be repeated simultaneously or within a few minutes apart.

Anion Gap

In plasma (serum), the number of cations must equal the number of anions to maintain electroneutrality. However, measurement of all of these cations and anions is not done routinely. Among all electrolytes, Na^+, K^+, Cl^-, and HCO_3^- are usually measured. From these measurements, the number of unmeasured anions can be calculated (Table 4.3). Generally, plasma [Na^+] exceeds the sum of plasma [Cl^-] and [HCO_3^-], and the difference is called the *anion gap* (AG). Since the change in serum [K^+] in either health or disease is minimal, this cation is not routinely included in the calculation of AG. Thus, AG is calculated as:

$$AG = \left(mEq/L \right) = \left[\left(Na^+ \right) - \left(Cl^- + HCO_3^- \right) \right]$$

Table 4.3 Unmeasured anions and cations (particularly anions)

Unmeasured cations (mEq/L)	Unmeasured anions (mEq/L)
K^+: 4.5	Albumin: 12
Ca^{2+}: 5.0 Mg^{2+}: 1.5	Other proteins: 3
	PO_4^{3-}: 2
	SO_4^{2-}: 1
	Organic acids 5
Total: 11	Total: 23
AG = 23–11 = 12 ± 4	

Normal AG Values

As shown in Table 4.3, the normal reference range for AG is 12 ± 4. This value was derived from older methods of electrolyte determinations using colorimetry and flame photometry. With the introduction of ion-selective electrode methodology, the normal AG levels are much lower, ranging from 3 to 11. These low values are related to high Cl^- determination. Variations in normal values of AG are frequently seen from laboratory to laboratory, and the clinician should follow his or her laboratory values for proper interpretation of AG in clinical medicine. For simplicity, an AG of 10 mEq/L is considered normal.

Hyperglycemia and AG

It is always debated whether or not AG should be calculated using measured serum Na^+ or corrected Na^+ in a patient with severe hyperglycemia. It is suggested that only measured Na^+ should be used for AG, and not the corrected Na^+. This suggestion is based on the assumption that Cl^- and HCO_3^- are equally diluted as Na^+ by movement of water from inside to outside of the cell caused by hyperglycemia. When AG is calculated using only corrected Na^+ and not corrected Cl^- and HCO_3^- for hyperglycemia, the AG is overestimated with the implication of underlying high AG metabolic acidosis. Na^+ decreases by 1.6 mEq/dL for each increase in 100 mg/dL glucose above normal glucose levels, but no such number is given for either Cl^- or HCO_3^-. It is, thus, emphasized that only measured Na^+ should be used to calculate the serum AG.

Clinical Use of AG

Traditionally, the AG is useful in classifying metabolic acidosis into high, normal, or low AG metabolic acidosis. High AG is due to accumulation of unmeasured anions, whereas normal AG is usually related to high Cl^- level. Low AG implies a substantial decrease in unmeasured anions, an increase in unmeasured cations, and spurious decrease in $[Na^+]$ or spurious increases in $[Cl^-]$ or $[HCO_3^-]$.

Mnemonic for High AG Metabolic Acidosis

The mnemonic to remember AG is GOLD MARK (glycols (ethylene and propylene glycols), oxoproline (pyroglutamic acid), L-lactate, D-lactate, methanol, aspirin, renal failure, ketoacidosis). Table 4.4 shows various causes of high AG metabolic acidosis.

Table 4.4 Most common causes of high AG metabolic acidosis

Cause	Unmeasured anions causing high AG
Uremic acidosis (renal failure)	Sulfate, phosphate, urate
Ketoacidosis (diabetes, starvation, alcohol)	Acetoacetate, β-hydroxybutyrate
Lactic acidosis	L-lactate
Small bowl resection	D-lactate
Intoxicants	
Methanol	Formate
Ethylene glycol	Glycolate, oxalate
Aspirin	Salicylate, L-lactate, ketoacids
Acetaminophen (Tylenol)	Pyroglutamate
Paraldehyde	Acetaldehyde or acetic acid
Toluene	Hippurate, benzoate

Table 4.5 Most common causes of normal AG metabolic acidosis

Cause	Mechanism
Diarrhea	Loss of HCO_3^- in stool
Ureterosigmoidostomy, ileal conduit	Loss of HCO_3^- in stool
Carbonic anhydrase inhibitors	Loss of HCO_3^- in urine
Recovery phase of ketoacidosis	Less HCO_3^- synthesis from decreased availability of ketones
Chronic kidney diseases (stages 4–5)	Decrease in NH_3 excretion
Proximal renal tubular acidosis (type II)	Loss of HCO_3^- in urine
Distal renal tubular acidosis (type I)	Decreased renal acid secretion
Distal renal tubular acidosis (type IV)	Decreased acid secretion and low NH_3 production
Dilutional acidosis	Increased Cl^- due to normal saline administration
Cholestyramine	Release of Cl^- in exchange for HCO_3^-

Normal AG Metabolic Acidosis

Table 4.5 shows causes for normal (hyperchloremic) AG metabolic acidosis

Low AG Metabolic Acidosis and Correction for Low Serum Albumin

Other than laboratory error, the most common cause of low AG acidosis in hospitalized patients is hypoalbuminemia. As shown in Table. 4.3, albumin is the major contributor for unmeasured anions and thus AG. A decrease in albumin from 4.0 to 2.0 g/dL reduces AG by 5.0 mEq/dL (for each gram decrease in albumin from normal value, the AG decreases by 2.5). Thus, a patient with chronic kidney disease (CKD) stages 4–5 and low albumin may seem to have a normal AG metabolic

Table 4.6 Most common causes of low AG metabolic acidosis

Cause	Mechanism
Hypoalbuminemia	Decreased number of anions
IgG myeloma	Increased number of cations
Bromide intoxication[a]	Bromide measured as chloride
Salicylate overdose	Salicylate measured as chloride
Hypercalcemia	Increased number of cations
Hypermagnesemia	Increased number of cations
Lithium toxicity	Increased number of cations
Hypertriglyceridemia	Different laboratory analysis

[a]Negative AG

acidosis, but when corrected for normal albumin, the acid–base disorder is a high AG metabolic acidosis. For example, the above patient with CKD stages 4–5 has a calculated AG of 12, albumin of 2.0 g/dL, and the laboratory reference AG of 10. This shows that the patient has only two excess anions (12–10 = 2). However, when AG is adjusted for hypoalbuminemia, the AG is 17, and Δ AG is 7 (17–10 = 7). Therefore, albumin levels should be obtained whenever an ABG is ordered, particularly in critically ill patients. Table 4.6 shows causes and possible mechanisms of low AG metabolic acidosis.

In addition to a decrease in unmeasured anions, an increase in unmeasured cations causes low AG. For example, A patient with IgG myeloma will have low AG because IgG molecules carry a positive charge at a pH of 7.4. Also, ingestion of bromide or iodine-containing medications or intoxication of these halides can raise the concentration of unmeasured anions and lower AG due to measurements of these halides as Cl^-. Salicylate overdose usually gives a negative AG, as high salicylate levels are measured as high Cl^- levels by certain chloride-sensitive ion-selective electrodes.

Occasionally, patients with severe hypertriglyceridemia may present with low AG due to a different laboratory measurement. Severe hypercalcemia, hypermagnesemia, or lithium toxicity may cause low AG. Some case reports demonstrated low AG in hypotonic hyponatremic patients. Thus, low AG is caused by many conditions.

Use of $\Delta AG/\Delta HCO_3^-$

Not only is AG useful in the classification of metabolic acidosis, but it is also indirectly helpful in analyzing mixed acid–base disorders such as high AG metabolic acidosis and metabolic alkalosis or high AG and normal AG metabolic acidosis. In a simple or uncomplicated high AG metabolic acidosis, the increase in AG above normal (called ΔAG) is equal to the decrease in HCO_3^- from normal value (called ΔHCO_3). In other words, for every 1 mEq/L rise in the AG, there is a concomitant fall of 1 mEq/L in HCO_3^-. This is defined as $\Delta AG/\Delta HCO_3^-$. In a simple high AG

metabolic acidosis, the $\Delta AG/\Delta HCO_3^-$ ratio is 1. Any significant deviation from 1 is indicative of a mixed acid–base disorder. For example, A patient with diarrhea typically develops a hyperchloremic or normal AG metabolic acidosis. In this condition, the decrease in HCO_3^- results in a reciprocal increase in Cl^- so that the AG does not change. As a result, the $\Delta AG/\Delta HCO_3^-$ ratio is 0. If this patient develops hypotension and subsequent lactic acidosis, the HCO_3^- decreases even further. In other words, the ΔHCO_3^- is greater than ΔAG, and the $\Delta AG/\Delta HCO_3^-$ ratio is <1 (above 0 but below 1), indicating a mixed high and normal AG metabolic acidosis.

In pure lactic acidosis, the $\Delta AG/\Delta HCO_3^-$ ratio is usually 1.6 because the lactate anions remain in the extracellular compartment because of low urinary excretion. This raises the AG. However, the HCO_3^- concentration does not decrease as non-HCO_3^- buffers participate in buffering lactate anions. In my opinion, the $\Delta AG/\Delta HCO_3^-$ ratio is usually not helpful in pure lactic acidosis, as lactate levels are available, and the $\Delta AG/\Delta HCO_3^-$ ratio varies from 0.8 to 1.8.

In a mixed high AG metabolic acidosis and metabolic alkalosis, the HCO_3^- level is inappropriately high relative to the increase in AG. As a result, the $\Delta AG/\Delta HCO_3^-$ ratio is >2.

Although the $\Delta AG/\Delta HCO_3^-$ ratio is a useful tool, it should not be used alone in identifying mixed acid–base disorders. Other pieces of evidence such as clinical information about the patient, normal AG range, AG corrected for albumin, and uncovering of hidden acid–base disorder during treatment should be taken into account whenever a mixed acid–base disorder is analyzed. Also, evaluation of volume status is important, as total HCO_3^- content in the ECF compartment may change. An example is diabetic ketoacidosis (DKA). Prior to development of DKA, the ECF water content in a 70 kg patient is 14 L, and the total HCO_3^- content is 336 mEq (14 L × 24 mEq/L = 336 mEq). DKA obligates water loss, and the patient develops volume depletion. As a result, water content decreases presumably to 10 L. At the same time, the HCO_3^- content decreases due to buffering of ketoacids presumably to 15 mEq/L. Now the new total HCO_3^- content is 150 mEq (10 L × 15 mEq = 150), a deficit of 186 mEq (336 mEq – 150 mEq = 186 mEq). Note that the AG continues to increase because of the addition of ketoacids, but the concentration of HCO_3^- decreases. As a result, the $\Delta AG/\Delta HCO_3^-$ ratio will be >2, suggesting the presence of spurious metabolic alkalosis. Thus, one must be cautious in interpreting the $\Delta AG/\Delta HCO_3^-$ ratio.

Secondary Physiologic Response (or Compensatory Response)

It is a physiologic process that minimizes changes in $[H^+]$ brought about by a primary change. In clinical practice, the term compensation rather than secondary physiologic response is usually used. Two types of compensatory responses (secondary physiologic responses) are involved: respiratory and renal. In a

metabolic acid–base disorder, the compensatory response is respiratory. For example, in metabolic acidosis, the primary change is a decrease in plasma [HCO_3^-] and an increase in [H^+]. The compensatory response is a decrease in pCO_2 due to hyperventilation. This decrease in pCO_2 limits the rise in [H^+], and thus the pH is returned to normal. The observed hyperventilation represents the normal physiologic response to an increase in [H^+]. Conversely, hypoventilation is an appropriate physiological response to metabolic alkalosis. In a respiratory acid–base disorder, the compensatory response is renal. In respiratory acidosis, the primary change is an increase in pCO_2, and a decrease in pH or an increase in [H^+]. The renal compensation increases the plasma [HCO_3^-] with a resultant increase in pH toward normal. It should be pointed out that these compensatory mechanisms do not increase the pH to normal but rather return the pH to normal.

Pathogenesis and Clinical Manifestations of Acid–Base Disorders

It is important to understand the development of acid–base disorders for proper interpretation of the primary acid–base disorder. The following pathophysiology underlies each of the four primary acid–base disorders.

Metabolic Acidosis

Causes Metabolic acidosis develops because of the following conditions:

1. Loss of HCO_3^- either from the GI tract or kidney
2. Retention of H^+ due to impaired renal function
3. Addition of exogenous or endogenous of strong acids

Clinical Manifestations

Metabolic acidosis affects almost all organ systems; however, following are the most important clinical manifestations (Table 4.7).

Metabolic Alkalosis

Metabolic alkalosis develops due to:

1. Retention of HCO_3^-
2. Loss of H^+

Table 4.7 Clinical manifestations of metabolic acidosis

Cardiovascular
Increased heart rate and contractility at pH <7.2
Decreased contractility at pH <7.1
Decreased cardiac responsiveness to catecholamines
Decreased renal and hepatic blood flow
Decreased fibrillation threshold
Increased peripheral vasodilation and hypotension
Neurologic
Increased sympathetic stimulation
Altered mental status
Increased cerebral blood flow
Decreased cerebral metabolism
Respiratory
Increased minute ventilation
Dyspnea
Decreased diaphragmatic contractility
Other
Inhibition of anaerobic metabolism
Increased protein catabolism
Increased metabolic rate
Impaired phagocytosis
Decreased ATP production
Impaired skeletal growth
Bone pain

Clinical Manifestations

Severe metabolic alkalosis affects several organ systems, including central nervous system, neuromuscular, cardiovascular, and pulmonary systems. In addition, several metabolic abnormalities have been reported. Table 4.8 summarizes these manifestations.

Acute Respiratory Acidosis

Acute respiratory acidosis results from retention of pCO_2 due to depression of medullary respiratory center, failure of motor functions of respiratory muscles and chest wall, airway obstruction, and ventilator defects.

Clinical Manifestations

Acute respiratory acidosis causes hypoxemia, resulting in several organ dysfunctions, as shown in Table 4.9.

Table 4.8 Clinical manifestations of metabolic alkalosis

Central nervous system
Reduction in blood flow
Confusion
Obtundation
Reduced seizure threshold
Neuromuscular
Increased excitability
Tetany
Cardiovascular
Reduced cardiac output
Reduced coronary blood flow
Arteriolar vasoconstriction
Increased heart rate
Predisposition to refractory ventricular and supraventricular arrhythmias
Pulmonary
Hypoventilation
Hypercapnia
Hypoxia
Metabolic
Hypokalemia
Decreased ionized Ca^{2+}
Hypophosphatemia
Hypomagnesemia
Stimulation of glycolysis and production of lactate

Table 4.9 Clinical manifestations of acute respiratory acidosis

CNS manifestations predominate and include the following:
1. Signs and symptoms: Nausea, vomiting, restlessness, headache, confusion, seizures, and coma
2. Cerebral blood flow: Increases acutely due to cerebral vasodilation of capillaries and venules. This cerebral vasodilation is mediated by nitric oxide
3. Intracranial pressure: Hypercapnia increases intracranial pressure due to increased blood volume and increased vascular pressure caused by vasodilation
Cardiac manifestations include an increase in blood pressure and heart rate secondary to increased sympathetic tone. Cardiac output increases. Also, coronary blood flow increases due to hypercapnia-induced vasodilation. Both peripheral vasodilation (due to hypercapnia) and vasoconstriction (due to increased sympathetic tone) occur in patients with acute respiratory acidosis. Arrhythmias are also common
Renal effects include renal vasodilation with mild hypercapnia and vasoconstriction at pCO_2 >70 mmHg. Renin–angiotensin II (AII)–aldosterone axis is stimulated by hypercapnia-induced sympathetic tone. Antidiuretic hormone (ADH) secretion is also increased
Other effects include skeletal muscle contraction, particularly diaphragmatic movement is reduced

Chronic Respiratory Acidosis

Chronic respiratory acidosis, similar to acute respiratory acidosis, is caused by (1) depression of medullary respiratory center; (2) failure of motor functions of respiratory muscles and chest wall; (3) ventilator defects; and (4) airway obstruction.

Clinical Manifestations

Table 4.10 shows pertinent clinical manifestations of chronic respiratory acidosis.

Acute Respiratory Alkalosis

With few exceptions, all causes are associated with both acute and chronic respiratory alkalosis. Acute respiratory alkalosis is generally caused by anxiety–hyperventilation syndrome, pain, acute illnesses such as pneumonia, acute asthmatic attack, septicemia, pulmonary embolism, pulmonary edema, salicylate ingestion, or increased minute ventilation in mechanically ventilated patients. Therefore, acute respiratory alkalosis is rather common in general wards and intensive care units.

When pCO_2 is lowered acutely, paresthesias of lower extremities, circumoral numbness, tingling of hands, mouth, and a feeling of chest tightness occur. Headache, light headedness, confusion, and disorientation are also common. Severe alkalosis may precipitate seizures and cardiac arrhythmias. These manifestations are related to central nervous system (CNS), cardiovascular, and metabolic effects. Table 4.11 shows the clinical manifestations of acute respiratory alkalosis.

Table 4.10 Clinical manifestations of chronic respiratory acidosis

Less severe compared with patients with acute respiratory acidosis because of near-normal pH
Hypoxemia and associated symptoms are common
CNS manifestations include tremors, ataxia, and poor appetite. Cerebral vasodilation and blood flow are increased but not to the extent of acute hypercapnia
Cardiovascular effects are pulmonary hypertension (cor pulmonale), peripheral edema, and supraventricular as well as ventricular arrhythmias. Cardiac output is normal or near normal
Normal GFR
Bone disease is present but less severe compared with metabolic acidosis. Hypercalciuria is also less common or absent in patients with respiratory acidosis

Table 4.11 Clinical manifestations of acute respiratory alkalosis

CNS effects
Acute hypocapnia causes sudden decrease in brain blood flow due to cerebral vasoconstriction. This results in a decrease in intracranial and intraocular pressures
1. Light headedness, confusion, and other manifestations are related to decreased cerebral perfusion
2. Electroencephalogram (EEG) changes such as slowing and high-voltage wave forms also occur
3. Acid–base changes are similar in both cerebrospinal fluid (CSF) and systemic blood during acute hypocapnia
4. Acral paresthesias are due to decreased blood flow to the skin
Cardiovascular effects
Acute hypocapnia decreases myocardial blood flow and O_2 supply.
1. Cardiac output is decreased
2. Coronary vasoconstriction and chest pain occur
3. Cardiac arrhythmias are common with severe hypocapnia
Metabolic effects
Lactate and ketoacid productions are increased
1. A decrease in plasma volume is observed
2. Acute hypocalcemia due to increased binding of Ca^{2+} can occur with precipitation of tetany and perioral tingling
3. Mild hyponatremia, hypokalemia, and hypophosphatemia may be present due to cellular shift

Chronic Respiratory Alkalosis

Individuals with chronic respiratory alkalosis are generally less symptomatic than subjects with acute respiratory alkalosis. Hyperventilation is subtle in many patients, and it is not even recognized by patients and clinicians. However, certain CNS, cardiovascular, and metabolic effects do occur in patients with chronic respiratory alkalosis. The following table (Table 4.12) shows the clinical manifestations of chronic respiratory alkalosis.

Approach to a Patient with an Acid–Base Disorder

With the above background, any acid–base disturbance can be approached with the following steps:

1. Measure electrolytes and ABG simultaneously or within few minutes apart
2. Check the validity of blood pH—use Henderson equation
3. Identify the primary disorder—use Table 4.1

4. Calculate the AG[1] (correct for low albumin, if indicated)
5. Identify the causes of the primary disorder
6. Calculate the expected compensation (also called secondary response)—use Table 4.13
7. Identify the mixed acid–base disorder, if any
8. Use $\Delta AG/\Delta HCO_3^-$ ratio appropriately
9. Determine the appropriate treatment

Table 4.12 Clinical manifestations of chronic respiratory alkalosis

CNS effects
1. CSF pH rises when pCO_2 is sufficiently low
2. CSF lactate levels may be high (alkalosis-induced)
3. Light headedness may be common
Cardiovascular Effects Common in individuals who climb mountains and live at high altitudes. These effects are:
1. Initially, cardiac output increases due to a decrease in peripheral vascular resistance
2. Heart rate goes up
3. Blood pressure remains normal secondary to decreased peripheral vascular resistance
4. Cardiac output returns to baseline 1–6 weeks after exposure to high altitude, but heart rate remains elevated
5. Blood flow to the kidneys and skin is reduced
6. Both blood and plasma volumes are reduced due to renal Na^+ loss; however, after several days of high altitude exposure, only blood volume returns to normal due to an increase in hemoglobin and hematocrit increase
7. All of the above manifestations are related to hypoxemia
Metabolic Effects In addition to low plasma volume, hyponatremia, hypokalemia, and hypophosphatemia due to cellular shifts are common. Decreased ionized Ca^{2+} is also common, causing tetany, Chvostek's and Trousseau's signs

Table 4.13 Normal compensatory responses to primary acid–base disorders

Acid–base disorder	Compensatory response
Metabolic acidosis	$pCO_2 = HCO_3 \times 1.5 + 8 \pm 2$ or for each mEq/L decrease in HCO_3^-, pCO_2 decreases by 1.2 mmHg
Metabolic alkalosis	For each mEq/L increase in HCO_3^-, pCO_2 increases by 0.7 mmHg
Respiratory acidosis	
Acute	For each mmHg increase in pCO_2, HCO_3^- increases by 0.1 mEq/L
Chronic	For each mmHg increase in pCO_2, HCO_3^- increases by 0.4 mEq/L
Respiratory alkalosis	
Acute	For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.2 mEq/L
Chronic	For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.4 mEq/L

[1] Urine AG, urine pH, and plasma osmolal gap will be discussed in other chapters.

How to Evaluate an Acid–Base Disorder

Example A 30-year-old man with a long history of intravenous drug abuse is admitted for weakness and abdominal pain. His respiratory rate is 24/min (normal = 12–14/min). Initial electrolyte and ABG values:

Na^+ = 136 mEq/L	pH = 7.28
K^+ = 5.1 mEq/L	pCO_2 = 30 mmHg
Cl^- = 100 mEq/L	pO_2 = 100 mmHg
HCO_3^- = 14 mEq/L	HCO_3^- = 13 mEq/L
BUN = 120 mg/dL	
Creatinine = 10 mg/dL	
Glucose = 90 mg/dL	

Step 1 Electrolytes and ABG were done simultaneously.

Step 2 Check the validity of blood pH.

Using the Henderson equation, we obtain:

$$\left[H^+ \right] (\text{nmol/L}) = 24 \times \frac{30}{14} = 51.4$$

From the section on Henderson equation, it is evident that the corresponding pH for the $[H^+]$ of 51.4 is approximately 7.28. Therefore, the reported pH for the patient is correct.

Step 3 Identify the primary disorder.

From Table 4.1, the primary disorder is metabolic acidosis because both pH and HCO_3^- are less than normal.

Step 4 Calculate the AG.

$$\left[\left(Na^+ \right) - \left(Cl^- + HCO_3^- \right) \right]$$

136− (100 + 14) = 22 (serum albumin not available)

Step 5 Identify the cause of the primary disorder.

As the AG is 22, this disorder is a high AG metabolic acidosis. From the causes listed in Table 4.4 and the laboratory values of the patient, it is evident that the cause is renal failure.

Step 6 Calculate the expected compensation.

Since hyperventilation is an appropriate compensatory (secondary physiologic response) response, the pCO_2 should be lower than the normal value of 40 mmHg.

This patient's pCO_2 is 30. The following formula is used to determine whether this value is the expected (or predicted) pCO_2 (Table 4.13).

$$\begin{aligned} pCO_2 &= HCO_3^- \times 1.5 + 8 \pm 2 \\ &= 14 \times 1.5 + 8 \pm 2 = 29 \end{aligned}$$

If the patient has an appropriate respiratory response for acidemia of 51.4 $[H^+]$, the expected pCO_2 should be between 27 and 31 mmHg. Since the patient's pCO_2 is 30, his respiratory response is appropriate. Therefore, the acid–base disturbance in this patient is a simple high AG metabolic acidosis with appropriate compensatory response.

If the patient's pCO_2 is different from the expected pCO_2, then a coexisting respiratory acid–base disorder is present. For example, if the patient's pCO_2 is lower than the expected pCO_2, a respiratory alkalosis is present in addition to metabolic acidosis. If, on the other hand, the patient's pCO_2 is higher than the expected pCO_2, a coexisting respiratory acidosis is present.

Step 7 Identify the mixed acid–base disorder, if any.

No mixed acid–base disorder is present (this step is not necessary in this patient, as step 6 revealed only one primary acid–base disorder).

Step 8 Use $\Delta AG/\Delta HCO_3^-$ ratio appropriately.

This step is not necessary in this patient.

Step 9 Determine the appropriate treatment.

Generally, the treatment for metabolic acidosis with pH < 7.20 is $NaHCO_3$. In this patient, the pH > 7.20, and thus no treatment is necessary. The patient is symptomatic from his renal failure and needs dialysis to relieve his symptoms. Dialysis will also improve his plasma $[HCO_3^-]$ and blood pH.

How to Evaluate a Mixed Acid–Base Disorder

It is not uncommon for two or three simple or primary acid–base disturbances to coexist in hospitalized patients. Mixed acid–base disorders should be suspected whenever (see Chap. 14 for details):

1. There is no compensatory response or overcompensation for a primary simple acid–base disorder
2. The pH and $[HCO_3^-]$ are normal, but the AG is high (mixed metabolic acidosis and metabolic alkalosis)
3. The pH is near normal, but $[HCO_3^-]$ is high (mixed metabolic alkalosis and respiratory acidosis)
4. The pH is near normal, but $[HCO_3^-]$ is low (mixed metabolic acidosis and respiratory alkalosis)
5. The pH is low (<7.4), but $[HCO_3^-]$ is normal (mixed metabolic acidosis and respiratory acidosis)

6. The pH is high (>7.4), but [HCO_3^-] is normal (mixed respiratory alkalosis and metabolic alkalosis)

Example A 31-year-old woman with AIDS is admitted for weakness and poor appetite. Her respiratory rate is 26/min. Lung examination reveals crackles bilaterally, and chest x-ray confirms pulmonary edema. Her electrolyte and ABG values are:

Na^+ = 129 mEq/L	pH = 7.36
K^+ = 3.4 mEq/L	pCO_2 = 22 mmHg
Cl^- = 90 mEq/L	pO_2 = 90 mmHg
HCO_3^- = 12 mEq/L	HCO_3^- = 11 mEq/L
BUN = 82 mg/dL	
Creatinine = 8.2 mg/dL	
Glucose = 100 mg/dL	

To analyze this acid–base disorder, follow the steps 1–9 discussed before.

Step 1 Labs and ABG are available.

Step 2 Check the validity of blood pH.

Using the Henderson equation, the [H^+] is 44, which corresponds to the pH of 7.36.

Step 3 Identify the primary disorder.

The dominant acid–base disturbance is metabolic acidosis because the pH is <7.40 and the HCO_3^- is <24 mEq/L.

Step 4 Calculate the AG.

The AG is 27, which is elevated.

Step 5 Identify the causes of the primary disorder.

From the laboratory values, the cause for the patient's metabolic acidosis is renal failure.

Step 6 Calculate the expected compensation.

For a simple metabolic acidosis, the expected pCO_2 is between 24 and 28 mmHg. However, the patient's pCO_2 is below 24, suggesting the coexistence of respiratory alkalosis. Thus, this patient has a mixed high AG metabolic acidosis and respiratory alkalosis.

Step 7 Identify the mixed acid–base disorder, if any.

This step is not necessary, as step 6 revealed the nature of the acid–base disorder.

Step 8 Use $\Delta AG/\Delta HCO_3^-$ ratio appropriately

Assuming normal AG is 10, ΔAG is 17, and ΔHCO_3^- is 12; therefore, the $\Delta AG/\Delta HCO_3^-$ ratio is 1.41. Thus, there is no hidden metabolic alkalosis in this patient.

Step 9 Determine the appropriate treatment.

Administration of $NaHCO_3$ to raise serum $[HCO_3^-]$ is not appropriate because of pulmonary edema. The appropriate treatment is renal replacement therapy such as hemodialysis, which not only removes fluid from the lungs but also increases serum $[HCO_3^-]$ and blood pH.

Hydration and Acid–Base Disorders-Induced Changes in Serum [Na+] and [Cl$^-$]

The normal serum $[Na^+]$ is 140 mEq/L, and serum $[Cl^-]$ is 100 mEq/L; therefore the ratio is 1.4:1. This ratio is maintained in states of hydration but altered in acid–base disorders.

Examples In hydration-induced conditions, serum $[Na^+]$ and serum $[Cl^-]$ should decrease or increase proportionately to maintain the normal ratio of 1.4:1, as follows:

Overhydration (*proportionate decrease in both*)

$$Na^+ \text{change}: 140 \rightarrow 126 \text{ mEq/L} = 14 \text{ mEq fall or } 10\% \text{ decrease}$$

$$Cl^- \text{change}: 100 \rightarrow 90 \text{ mEq/L} = 10 \text{ mEq fall or } 10\% \text{ decrease}$$

Dehydration (*proportionate increase in both*)

$$Na^+ \text{change}: 140 \rightarrow 154 \text{ mEq/L} = 14 \text{ mEq rise or } 10\% \text{ increase}$$

$$Cl^- \text{change}: 100 \rightarrow 110 \text{ mEq/L} = 10 \text{ mEq/L rise or } 10\% \text{ increase}$$

On the other hand, a change in $[Cl^-]$ without a change in $[Na^+]$ always represents a disturbance in acid–base alone. Therefore, the ratio of 1.4:1 is disturbed, as follows:

Metabolic alkalosis or respiratory acidosis (*disproportionate decrease in Cl$^-$ compared to Na$^+$*)

$$Na^+ \text{change}: 140 \rightarrow 140 \text{ mEq/L} = 0 \text{ mEq change or } 0\% \text{ change}$$

$$Cl^- \text{change}: 100 \rightarrow 90 \text{ mEq/L} = 10 \text{ mEq/L fall or 10\% decrease}$$

Respiratory alkalosis or hyperchloremic acidosis (*disproportionate increase in Cl^- compared to Na^+*)

$$Na^+ \text{change}: 140 \rightarrow 140 \text{ mEq/L} = 0 \text{ mEq change or 0\% change}$$

$$Cl^- \text{change}: 100 \rightarrow 110 \text{ mEq/L} = 10 \text{ mEq/L rise or 10\% increase}$$

Based on the above examples, one can follow the changes in serum [Na^+] and [Cl^-] in combined conditions of disturbed hydration and acid–base disorders.

Overhydration and metabolic alkalosis (*disproportionate decrease in both; fall in Cl^- is additive*)

$$Na^+ \text{change}: 140 \rightarrow 126 \text{ mEq/L} = 14 \text{ mEq fall or 10\% decrease}$$

$$Cl^- \text{change}: 100 \rightarrow 80 \text{ mEq/L} = 20 \text{ mEq/L fall or 20\% decrease}$$

Dehydration and metabolic alkalosis (*disproportionate increase in both; rise in $Na^+ > Cl^-$*)

$$Na^+ \text{change}: 140 \rightarrow 168 \text{ mEq/L} = 28 \text{ mEq rise or 20\% increase}$$

$$Cl^- \text{change}: 100 \rightarrow 90 \text{ mEq/L} = 10 \text{ mEq/L fall or 10\% decrease}$$

Study Questions

Case 1 A 50-year-old man is admitted to the intensive care unit with anterior wall myocardial infarction. Six hours later, he develops shortness of breath. Physical examination and chest x-ray are consistent with pulmonary edema. Electrolytes and ABG values:

Na^+ = 140 mEq/L	pH = 7.36
K^+ = 5.2 mEq/L	pCO_2 = 34 mmHg
Cl^- = 94 mEq/L	pO_2 = 80 mmHg
HCO_3^- = 16 mEq/L	HCO_3^- = 22 mEq/L
BUN = 30 mg/dL	
Creatinine = 1.4 mg/dL	
Glucose = 200 mg/dL	

Question 1 Which one of the following BEST characterizes the acid–base disturbance?

A. Metabolic acidosis and respiratory alkalosis
B. Metabolic alkalosis and metabolic acidosis
C. Respiratory acidosis and metabolic acidosis
D. Respiratory alkalosis and metabolic alkalosis
E. None of the above

The answer is E. The acid–base disorder should be analyzed systematically. Once the labs are available, the next step is to check whether the pH is correct or not. One must use the Henderson equation to obtain the $[H^+]$ and then the pH. The Henderson equation is:

$$\left[H^+\right] = 24 \times \frac{pCO_2}{HCO_3^-}$$

Substituting the values, we obtain:

$$\left[H^+\right] = 24 \times \frac{34}{16} = 51$$

The $[H^+]$ of 51 corresponds to a pH of 7.30. Therefore, the pH reported from the lab is incorrect. Also, there is a large difference between the measured and calculated HCO_3^-. In view of this, it is difficult to interpret the ABG. Both electrolytes and ABG should be repeated within few minutes apart. This case emphasizes the need for checking the accuracy or internal consistency of the pH.

Case 2 A 42-year-old man is admitted because of dizziness and weakness. His blood pressure is 120/80 mmHg with a pulse rate of 90 beats/min (sitting) and 100/64 mmHG with a pulse rate of 110 beats/min (standing). He is not on any medications but admits to vomiting. Admitting electrolyte and ABG values:

Na^+ = 129 mEq/L	pH = 7.53
K^+ = 2.5 mEq/L	pCO = 63 mmHg
Cl^- = 58 mEq/L	pO_2 = 62 mmHg
HCO_3^- = 58 mEq/L	HCO_3^- = 58 mEq/L
Creatinine = 1.9 mg/dL	
BUN = 32 mg/dL	
Glucose = 94 mg/dL	

Question 1 Analyze the acid–base disturbance (use steps that are necessary).

Answer To analyze this acid–base disorder, follow the appropriate steps that are necessary.

Step 1 Check the validity of pH.

According to the Henderson equation, the $[H^+]$ is 26, which corresponds to a pH of 7.53. Therefore, the reported pH is correct.

Step 2 Identify the primary disorder.

From Table 27.1, the primary acid–base disturbance is metabolic alkalosis.

Step 3 Calculate the AG.

The AG is 13, which is normal (calculate AG in all primary acid–base disorders so that the hidden metabolic acidosis is not missed).

Step 4 Identify the cause of the primary disorder.

The cause for metabolic alkalosis is vomiting.

Step 5 Calculate the expected compensation.

The respiratory compensation is appropriate (Table 4.13), suggesting that this acid–base disturbance is a simple metabolic alkalosis.

Question 2 How would you treat this acid–base disturbance?

Answer The treatment is normal saline with KCl supplementation.

Case 3 A 72-year-old woman with a history of type 2 diabetes mellitus, congestive heart failure (CHF), and renal failure is admitted for nausea, vomiting, and shortness of breath. Her medications include insulin and furosemide. Her weight is 60 kg. Admission electrolyte and ABG values:

Na^+ = 140 mEq/L	pH = 7.40
K^+ = 4.1 mEq/L	pCO_2 = 40 mmHg
Cl^- = 95 mEq/L	pO_2 = 90 mmHg
HCO_3^- = 24 mEq/L	HCO_3^- = 24 mEq/L
Creatinine = 4.1 mg/dL	
BUN = 52 mg/dL	
Glucose = 145 mg/dL	

Question 1 Characterize the acid–base disturbance in this patient.

Answer The electrolytes and ABG values reveal no abnormalities. However, a step-by-step approach reveals that a mixed acid–base disturbance is present.

Step 1 Check the validity of pH.

From the Henderson equation, the $[H^+]$ is 40 nmol/L, which is equal to a pH of 7.40.

Step 2 Identify the primary disorder.

From ABG values, no apparent acid–base disturbance is present.

Step 3 Calculate the AG.

The AG is 21, which suggests the presence of a high AG metabolic acidosis (this case signifies the importance of calculating AG).

Step 4 Identify the cause of the primary disorder.

The cause for this metabolic acidosis is renal failure.

Step 5 Calculate the expected compensation.

If this were a pure metabolic acidosis, the pH, serum [HCO_3^-], and pCO_2 levels would be lower than normal. Since the patient has vomiting and she is also taking furosemide for her CHF, she developed metabolic alkalosis. The coexistence of metabolic acidosis and metabolic alkalosis normalizes ABG values and gives the impression of no underlying disturbance. The clue for the diagnosis of this mixed metabolic acidosis and metabolic alkalosis is the presence of a high AG. Thus, this case emphasizes the importance of calculating AG in the analysis of any acid–base disturbance.

Question 2 How would you manage her?

Answer Since she has shortness of breath due to CHF, i.v. furosemide can be tried. If the patient fails to respond, nesiritide can be started alone or in combination with dobutamine. If still unresponsive, 2–3 treatments of hemodialysis can improve her CHF (the patients symptoms were relieved by two treatments of hemodialysis with low blood flow).

Case 4 A 65-year-old man with a history of chronic obstructive pulmonary disease (COPD) is admitted for management of shortness of breath. On admission, his electrolyte and ABG values:

Na^+ = 134 mEq/L	pH = 7.35
K^+ = 3.6 mEq/L	pCO_2 = 64 mmHg
Cl^- = 90 mEq/L	pO_2 = 70 mmHg
HCO_3^- = 34 mEq/L	HCO_3^- = 33 mEq/L
Creatinine = 1.1 mg/dL	
BUN = 12 mg/dL	
Glucose = 100 mg/dL	

Question 1 Characterize the acid–base disorder.

Answer As earlier, follow the step-by-step method to analyze this acid–base disorder.

Step 1 Check the validity of pH.

According to the Henderson equation, the $[H^+]$ is 45 nmol/L, which corresponds to a pH of 7.35.

Step 2 Identify the primary disorder.

From Table 4.1, the primary acid–base disturbance is respiratory acidosis.

Step 3 Calculate the AG.

The AG is 10, which is normal.

Step 4 Identify the cause of the primary disorder.

The cause for this patient's respiratory acidosis is COPD.

Step 5 Calculate the expected compensation.

The compensation for respiratory acidosis is renal reabsorption of HCO_3^-. From Table 4.13, the patient has a primary chronic rather than acute respiratory acidosis.

Step 9 Determine the appropriate treatment.

The immediate treatment is administration of oxygen by nasal cannula and subsequent correction of the precipitating factor.

Case 5 A 51-year-old man is admitted for painless mass in right temporal area for a 3-week period. The only complaint he had was poor appetite with 4 lb. weight loss. He has no history of any other chronic disease and was not on any medications. He has not seen a physician in 10 years. Admitting electrolyte and ABG values:

Na^+ = 124 mEq/L	pH = 7.39
K^+ = 3.9 mEq/L	pCO_2 = 39 mmHg
Cl^- = 100 mEq/L	pO_2 = 94 mmHg
HCO_3^- = 23 mEq/L	HCO_3^- = 22 mEq/L
Creatinine = 1.0 mg/dL	
BUN = 16 mg/dL	
Glucose = 102 mg/dL	
Serum osmolality = 284 mOsm/kg H_2O	

Question 1 What is the most clinically evident abnormality in the assessment of acid–base disturbance in this patient?

Answer Calculation of AG is extremely important in this patient. From the electrolytes, it is obvious that the AG is only 1. This is abnormal that warrants further evaluation. Hyponatremia does not lower AG to this extent.

Question 2 What other test is helpful in the analysis of low AG?

Answer Serum albumin is the most common cause of low AG in hospitalized and also in ambulatory patients. Serum albumin level came back as 4.5 g/dL. Therefore, hypoalbuminemia is not the cause for his low AG.

Question 3 What other lab test is pertinent in view of hyponatremia and normal serum osmolality?

Answer Ordering serum total protein is very important at this time. His total protein is 14.2 g/dL, which is elevated.

Serum and urine protein immunoelectrophoresis showed very high IgG levels, suggesting IgG multiple myeloma.

Question 4 How does IgG myeloma cause low AG?

Answer IgG molecules carry a positive charge at pH of 7.40 and thus an increase in unmeasured cations. From Table 4.6, it is evident that an increase in unmeasured cations causes low AG.

Suggested Reading

Abelow B. Understanding acid-base. Baltimore: Williams & Wilkins; 1997.
Adrogué HJ, Gennari JF, Galla JH, et al. Assessing acid–base disorders. Kidney Int. 2009;76:1239–47.
DuBose TD. Disorders of acid-base balance. In: Skorecki K, et al., editors. Brenner & Rector's the kidney. 10th ed. Philadelphia: Elsevier; 2016. p. 511–58.
Emmett M. Approach to the patient with a negative anion gap. Am J Kidney Dis. 2016;67:143–50.
Gennari JF, Adrogué HJ, Galla JH, Madias NE. Acid-Base disorders and their treatment. Boca Raton: Taylor & Francis; 2005.
Kamel KS, Halperin ML. Fluid, electrolyte, and acid-base physiology. A problem-based approach. 5th ed. Philadelphia: Elsevier, Inc; 2017.
Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. Clin J Am Soc Nephrol. 2007;2:162–74.
Kurtz I. Acid-Base case studies. 2nd ed. Victoria: Trafford Publishing; 2006.
Wesson DE, editor. Metabolic acidosis. A guide to clinical assessment and management. New York: Springer; 2016.

Chapter 5
Lactic Acidosis

Although lactic acid and lactate are used interchangeably, it is the latter that circulates predominantly in the body at pH of 7.4. Lactate occurs in two stereoisomers or enantiomers: L-lactate and D-lactate (Fig. 5.1). L-lactate is the predominant stereoisomer in healthy subjects. D-lactate is usually synthesized from bacteria. In clinical laboratories, only L-lactate (simply lactate) is measured.

Lactate is formed from pyruvate, which is an intermediate metabolic product of anaerobic glycolysis. Thus, the major source of lactate is glucose. Another source of lactate production is alanine (16–20%), which is converted to pyruvate via alanine aminotransferase (Fig. 5.2). Pyruvate then enters the citric acid cycle and oxidized to form CO_2 and water (Fig. 5.2). During this process, ATP is generated. Glycolysis occurs in cytoplasm, whereas oxidation occurs in mitochondria. Lactate is also converted into glucose via gluconeogenesis. Thus, lactate is cleared from body by its conversion to pyruvate and glucose.

Approximately 20 mmol/kg/day of lactate is produced (~1300 mmol in a 70 kg man) in tissues such as skin (350 mmol), erythrocytes (302 mmol), brain (235 mmol), skeletal muscle (218 mmol), GI tract (115 mmol), and platelets and white blood cells (70 mmol). Lactate is utilized (metabolized) in the liver (722 mmol), kidney (386 mmol), heart (80 mmol), and other organs (102 mmol). Despite this high daily production of lactate, its circulating levels remain <1.5 mmol/L because of extensive utilization, as stated above. Lactic acidosis develops only when lactate production exceeds its utilization or when utilization of lactate is greatly reduced despite normal production, as in liver failure.

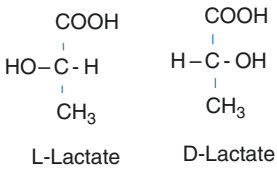

Fig. 5.1 Stereoisomers of lactate

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_5

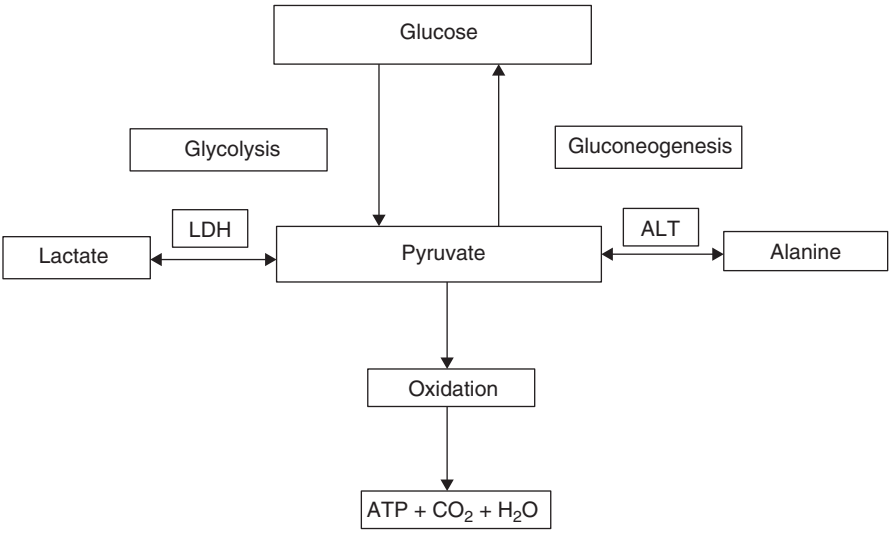

Fig. 5.2 Simplified diagram illustrating lactate formation from pyruvate occurring via glycolysis (cytoplasm) and oxidation of pyruvate to CO_2 and water (mitochondria). LDH lactate dehydrogenase, ALT alanine aminotransferase

Lactic acidosis is a serious condition and carries increased morbidity and mortality. There is a linear relationship between lactate levels and mortality, and higher levels predict mortality. There are two types of lactic acidosis. The most common one is L-lactic acidosis, and less frequent one is D-lactic acidosis, and both types are presented below.

L-Lactic Acidosis

Production

As stated above, lactate is formed only from pyruvate (Fig. 5.2). This conversion is facilitated by lactate dehydrogenase (LDH). In this reaction, pyruvate is reduced to lactate, which requires oxidation of reduced nicotinamide adenine dinucleotide (NADH) to oxidized nicotinamide adenine dinucleotide (NAD^+). NADH/NAD^+ ratio determines the conversions between pyruvate and lactate. The normal lactate to pyruvate ratio is 10:1. As shown in the reaction below, lactate can be oxidized to pyruvate by LDH where NAD^+ is reduced to NADH

$$\text{Pyruvate} + \text{NADH} + H^+ \xleftrightarrow{\text{LDH}} \text{Lactate} + NAD^+$$

From the above reaction, excess lactate production can be expected by the following pathophysiologic processes:

1. Increased glycolysis and pyruvate production, which are caused by intravenous (i.v.) glucose or epinephrine infusion, and metabolic or respiratory alkalosis. Alkalosis stimulates glycolysis by increasing the activity of a rate-limiting enzyme of glycolysis, phosphofructokinase (PFK). Acidosis and ATP inhibit PFK, leading to less lactate production
2. An increase in NADH/NAD^+ ratio due to hypoxic conditions
3. Combination of above two processes

Hyperlactatemia Vs. Lactic Acidosis

Hyperlactatemia is defined as serum lactate levels of 2–5 mmol/L without acidosis. It usually occurs in conditions of adequate tissue perfusion and tissue buffering capacity. Hyperlactatemia is seen in conditions of activated aerobic glycolysis due to stress, elevated epinephrine levels with the use of β_2-adrenergic agonists, asthma, alkalemia, and certain cytokine-stimulated glycolysis. Some drugs (antiretrovirals) may also cause hyperlactatemia. Serum [HCO_3^-] may be slightly lowered by increased lactate levels, but the systemic pH may be minimally altered. Removal of offending agent or correction of clinical condition may improve hyperlactatemia.

In contrast to hyperlactatemia, lactic acidosis is seen in patients with global tissue hypoxia and is associated with severe consequences. Normalization of lactate levels is rather difficult (see Treatment).

Causes

Causes can be either acquired or inherited. Most of the causes in adults are acquired (see Tables 5.1 and 5.2).

1. Generally, lactic acidosis is divided into two types: type A and type B acidosis
2. Type A acidosis results from generalized or regional tissue hypoxia
3. Type B acidosis results from biochemical abnormalities due to systemic diseases or toxins. Based on the underlying etiology, some authorities may divide type B lactic acidosis into type B1 (systemic diseases), type B2 (drugs and toxins), and type B3 (inherited)
4. Note that both type A and type B conditions can be superimposed on one another rather commonly in any patient (metformin use in CHF patient)

Table 5.1 Causes of type A lactic acidosis (clinical evidence of tissue hypoxia)

Cause	Mechanism(s)
Shock	
Septic shock	Hypotension
Hypovolemic shock	↓ O_2 delivery, ↑ glycolysis, ↓ ATP, ↑ pyruvate production→ ↑ lactic acid production
Cardiogenic shock	↓ O_2 delivery, ↑ glycolysis, ↓ ATP, ↑ pyruvate production→ ↑ lactic acid production
Hemorrhagic shock	↓ O_2 delivery, ↑ glycolysis, ↓ ATP, ↑ pyruvate production→ ↑ lactic acid production
Severe tissue hypoxia	↓ O_2 delivery, ↑ glycolysis, ↓ ATP, ↑ pyruvate production→ ↑ lactic acid production
Severe regional hypoperfusion due to hypotension	↓ O_2 delivery, ↑ glycolysis, ↓ ATP, ↑ pyruvate production→ ↑ lactic acid production
Severe anemia (<4.0 g/dL)	Tissue hypoxia
Severe asthma	Respiratory alkalosis stimulation of glycolysis and lactate production, tissue hypoxia, β-adrenergic stimulation, and lactate production
Carbon monoxide poisoning	Carbon monoxide binds more avidly to Hgb than O_2, leading to less delivery to tissues and hypoxia, inhibition of electron transport system, ↓ ATP, ↑ anaerobic glycolysis

Table 5.2 Causes of type B lactic acidosis (no clinical evidence of tissue hypoxia)

Causes	Mechanism(s)
Systemic disease (B1)	
Liver disease	↓ Lactate metabolism, ↓ pyruvate dehydrogenase complex (PDC)[a] activity, respiratory alkalosis, and hypoglycemia may precipitate lactate production
Diabetes mellitus	Presence of microvascular disease and atherosclerosis compromising circulation, drug use such as metformin, ↓ PDC activity
Renal failure and renal replacement therapies	Stimulation of lactate production by alkalinization due to HCO_3^-, dialysate baths containing lactate
Malignancy	Lymphomas, leukemias, and carcinomas (breast, lung, colon, pancreas), production of lactate by tumor cells via ↑ anaerobic glycolysis, ↑ cytokine production, hypoxia-inducible factor
ATP depletion	↑ Anaerobic glycolysis
Thiamine deficiency	Inhibits PDC activity, thereby limiting glucose metabolism to glycolysis only
Seizures	Increased muscle activity, compromised blood flow, and tissue hypoxia
Hypoglycemia	Inhibits lactate uptake by liver, ↑ epinephrine release causing increased production of pyruvate
Drugs/toxins (B2)	
Metformin	Promotes lactate production from glucose in small intestine, ↑ $NADH/NAD^+$ ratio, inhibits gluconeogenesis from lactate, inhibition of mitochondrial oxidative phosphorylation, patients with renal, hepatic, and cardiac failure are at risk

(continued)

Table 5.2 (continued)

Causes	Mechanism(s)
Ethanol	Impairs gluconeogenesis from lactate to glucose, depletes NAD^+ favoring lactate accumulation
Methanol	Toxic products of methanol (formaldehyde, formic acid) inhibits oxidative phosphorylation and ATP synthesis
Ethylene glycol	↑ NADH/NAD^+ ratio during metabolism of ethylene glycol via alcohol dehydrogenase
Propylene glycol	Used as solvent (during infusion of lorazepam, nitroglycerine, or topical application of silver sulfadiazine), produces lactate during its metabolism via alcohol dehydrogenase. This reaction produces high NADH/NAD^+ ratio
Salicylates	Respiratory alkalosis-stimulated lactate production, inhibition of oxidative phosphorylation
Cyanide poisoning	Inhibition of oxidative phosphorylation, ↓ ATP production, ↑ glycolysis, ↑ NADH/NAD^+ ratio, leading to pyruvate conversion to lactate production
Catecholamines	Epinephrine increases glycolysis and inhibits pyruvate formation from lactate. Increased vasoconstriction of skin, skeletal muscle, and splanchnic circulation with high concentrations of epinephrine and norepinephrine. Lactic acidosis may be the initial finding in pheochromocytoma
Cocaine	Increased vasoconstriction
Antiretrovirals (didanosine, zidovudine, stavudine, tenofovir)	Inhibition of mitochondrial DNA synthesis, ↓ ATP production, ↑ glycolysis
Linezolid	Mitochondrial toxicity
Propofol	Sedative, increased production of lactate on high doses due to uncoupling of oxidative phosphorylation
Hereditary or acquired enzyme defects (B3)	(see below)

[a]Pyruvate dehydrogenase complex is an enzymatic system that converts pyruvate to acetyl-CoA in mitochondria and hence to CO_2 and H_2O via citric acid cycle

Selected Conditions of L-Lactic Acidosis

Tissue Hypoxia The most important cause of type A lactic acidosis is tissue hypoxia, which may be due to decreased perfusion or decreased O_2 content. Shock of any etiology leads to hypotension, leading to lactic acid production. Other causes of tissue hypoxia include severe anemia, severe asthma, and carbon monoxide poisoning.

Sepsis and septic shock are due to macro- and microcirculatory dysfunction with decreased O_2 and nutrient delivery to the peripheral tissues. The resultant hypoxia causes inhibition of mitochondrial oxidative phosphorylation and reduction in ATP synthesis as well as an increase in NADH/NAD^+ ratio. This causes high lactate production, which is considered a useful marker of tissue hypoxia and a plan for fluid resuscitation in sepsis and septic shock.

During sepsis, insulin resistance occurs and gluconeogenesis increases. Also, whole-body glucose uptake by noninsulin-mediated mechanisms occurs. Glucose uptake by tissues such as skeletal muscle is mediated by cytokines such as tumor necrosis factor α and interleukin 6. Insulin resistance, gluconeogenesis, and cytokine stimulation of glucose uptake promote glycolysis and production of lactate from pyruvate.

Although elevated levels of lactate from anaerobic glycolysis due to tissue hypoxia have been reported to carry poor prognosis in sepsis, it was proposed that hyperlactatemia may also be caused by aerobic (not related to hypoxia) glycolysis. For example, sepsis causes high circulating levels of epinephrine, which stimulates Na/K-ATPase of skeletal muscle membrane and causes increased aerobic glycolysis. Thus, a major portion of the increased lactate levels may be attributed to aerobic glycolysis. This suggests that lactate is an unreliable marker of sepsis. Despite this critique, lactate is simple to measure, and its increasing levels during uncontrolled sepsis and decreasing levels to antibiotic therapy make it a dependable marker for sepsis.

Malignancy In 1923, Otto Warburg demonstrated that cancer cells have the ability to increase their glycolytic activity and generate excessive production of lactic acid in the presence of O_2. This phenomenon of aerobic glycolysis was subsequently named "Warburg effect." Otto Warburg also observed that glucose uptake by tumor cells was much higher than normal cells and tumor cells metabolized more glucose to lactate. Indeed it was found that lactate levels were much higher in blood vessels leaving the tumor cells than blood vessels entering the tumor cells. Later, it was observed that hematologic malignancies such as lymphomas and leukemias generate very high levels of lactic acid. Patients with very high levels of lactic acid had poor prognosis. Other malignancies, including melanomas, multiple myeloma, lung cancer, sarcomas, breast cancer, as well as others, were also found to generate and release lactic acid into the surrounding environment.

Several mechanisms for increased production of lactic acid by cancer cells have been demonstrated:

1. Glucose uptake by cancer cells is enhanced. Insulin-like growth factor-1 and tumor necrosis factor α, which are increased by cancer cells, stimulate glucose uptake
2. Hexokinase and other glycolytic enzymes are overexpressed in many tumors
3. Expression of transcription factors such as hypoxia-inducible transcription factor-1 (HIF-1) and c-Myc is enhanced in several cancer tissues. HIF-1 activates the genes encoding glycolytic enzymes, glucose, and lactate transporters, leading to enhanced glycolysis and lactic acid production
4. HIF-1 indirectly inhibits pyruvate dehydrogenase (PDH), which converts pyruvate to acetyl-CoA for mitochondrial oxidation, thereby driving the accumulated pyruvate to lactate
5. Thiamine deficiency caused by tumor cells and chemotherapy (methotrexate). Thiamine is a cofactor for PDH, and its deficiency causes decreased oxidative phosphorylation and energy (ATP) production

Lactic acid that is accumulated in cancer cells is transported from inside to outside by proton-linked monocarboxylate transporters (MCTs). Of the 14 MCT isoforms, only MCT1 and MCT4 are involved in lactic acid transport. Lactate, pyruvate, β-hydroxybutyrate, and acetoacetate are short-chain monocarboxylates. Once lactic acid is outside the cell, the pH of the extracellular microenvironment becomes severely acidic (in the range of 6.6), which promotes progression of tumor and imparts poor prognosis in several human cancers. MCT1 and MCT4 stimulate glycolysis in cancer cells in addition to their participation in lactic acid transport. Thus, inhibitors of MCT1 and MCT4 may decrease aerobic glycolytic pathway and lower lactate production. In addition to high activity of MCTs, increased activity of lactate dehydrogenase that converts pyruvate to lactate has been reported in cancer cells.

Treatment as well as prevention of malignancy-induced excess lactic acid is currently limited. Thiamine administration may be helpful. Also, inhibitors of lactate dehydrogenase and MCTs, once available, may play a significant role in preventing excess production of lactic acid in various human cancers.

Metformin-Associated Lactic Acidosis (MALA) Metformin is a biguanide and is the recommended choice of oral hypoglycemic agent for patients with type 2 diabetes. Despite its widespread use, the occurrence of severe or fatal lactic acidosis is rather uncommon. The incidence of lactic acidosis at therapeutic levels of metformin is 3–5 cases per 100,000 patient years. Metformin lowers glucose by inhibition of hepatic gluconeogenesis and promoting glucose uptake by skeletal muscle. Additional mechanisms include interaction with the incretin axis through the action of glucagon-like peptide 1 and also antagonizing the actions of glucagon. Metformin is considered safe if used properly. Most of the drug is metabolized by the kidney with partial fecal elimination. Therefore, the dose requirements in patients with severe renal failure are different compared to a patient with normal renal function.

MALA or hyperlactatemia without acidosis develops in patients with certain risk factors such as severe renal impairment, dehydration, alcohol use, sepsis, shock, tissue hypoxia, and elderly patients due to decreased renal function. In these conditions, the metformin levels are usually higher than the therapeutic levels.
The major mechanism for MALA is the inhibition of mitochondrial oxidative phosphorylation. This inhibition occurs as follows. When metformin levels increase, the drug binds to the mitochondrial membrane and inhibits the complex I (NADH:ubiquinone oxidoreductase). As a result, $NADH^+$ is not oxidized to NAD^+, and the electrons generated during this conversion are not supplied to complex I. The accumulated $NADH^+$ conversion of pyruvate to lactate in the cytoplasm is increased (see the reaction under production of lactate). Direct binding of metformin seems to occur via mitochondrial copper ion. Higher doses of metformin seem to decrease the activity of pyruvate dehydrogenase, causing decreased entry of pyruvate to form acetyl-CoA.

Once MALA is diagnosed with elevated serum levels of metformin, renal replacement therapy (RRT) should be instituted. Aside from supportive care, conventional hemodialysis is the preferred approach, if the patient is hemodynamically stable. If the patient is unstable, efficient continuous venovenous hemofiltration or

hemodiafiltration can be used to remove metformin. RRT is a life-saving procedure for patients with MALA.

Antiretroviral Agents Hyperlactatemia rather than severe lactic acidosis is common with nucleoside reverse transcriptase inhibitors (NRTIs) such as didanosine, zidovudine, stavudine, lamivudine, abacavir, and tenofovir. These NRTIs inhibit mitochondrial γ-polymerase and cause depletion of mitochondrial DNA. This leads to decreased mitochondrial function and impaired oxidative phosphorylation. The conversion of pyruvate to acetyl-CoA is decreased with resultant accumulation of pyruvate in cytosol. Subsequently, lactic acid is generated from pyruvate.

The prevalence of asymptomatic hyperlactatemia (2–5 mmol/L) ranges from 15% to 35% of HIV patients treated with NRTIs. The incidence of severe lactic acidosis (>5 mmol/L) is 1.7–25.2 cases per 1000 person-years. Severe acidosis with lactate levels >10 mmol/L carries a mortality rate from 30% to 60%.

Management of lactic acidosis due to antiretroviral agents is similar to that of other etiologies. Discontinuation of the drug is the first step in the management of severe lactic acidosis followed by other supportive measures, including appropriate fluids, $NaHCO_3$ as needed (pH <7.15), thiamine, riboflavin, L-carnitine, and coenzyme Q. Renal replacement therapy has also been used with variable success.

Linezolid The first commercially available oxazolidinone antibiotic, linezolid, was approved for use in 2000. It is frequently used to treat vancomycin-resistant enterococcus and other gram-positive organisms. It is also used as a second-line therapy for mycobacterial infections. One of the adverse effects of linezolid is lactic acidosis. Linezolid inhibits bacterial protein synthesis. Similarly, it inhibits mitochondrial protein synthesis, thereby inhibiting mitochondrial function. More specifically, inhibition of complex IV was observed. Decreased mitochondrial activity by linezolid was reported in many studies, and the inhibition seems to be dose-dependent. Thus, long-term users of linezolid are at greater risk severe lactic acidosis.

Some risk factors for linezolid-induced lactic acidosis have been reported. It was found that patients with mitochondrial DNA polymorphism A2706G are predisposed to linezolid-induced lactic acidosis. Also, concomitant use of drugs such as selective serotonin reuptake inhibitors may precipitate lactic acidosis.

Treatment includes discontinuation of the drug, which is sufficient to resolve the acidosis. Factors such as thiamine, riboflavin, L-carnitine, and coenzyme Q have also been used. In selected cases, renal replacement therapy was also employed to facilitate the removal of linezolid to improve lactic acidosis.

Propofol It is widely used in children and adults as a sedative and anesthetic agent because of its rapid onset and short duration of action. It also has anticonvulsive properties. It has been reported that infusion of the drug for >48 h and high doses (>4 mg/kg/h) causes a rare complication called propofol infusion syndrome (PRIS). This syndrome is characterized by metabolic acidosis due to lactic acid, bradycardia, hypotension, cardiac failure, rhabdomyolysis, and death.

The pathophysiology is not completely understood, but genetic predisposition, mitochondrial dysfunction, and increases in serum free fatty acids have been impli-

cated. Use of catecholamines and corticosteroids may trigger the development of PRIS. Animal studies have shown that propofol uncouples oxidative phosphorylation and decreases the functions of complexes II, complex III, and coenzyme Q with resultant low energy production. Accumulation of pyruvate leads to lactic acid production.

Clinical features of high lactic acid and CK level, bradycardia, and hypotension in any patient on high doses of propofol for >48 h should be suspicious for early development of PRIS. Treatment includes discontinuation of propofol and appropriate measures for other complications. Renal replacement therapy is required for management of hyperkalemia and acute kidney injury due to rhabdomyolysis.

Lactic Acidosis Due to Hereditary or Acquired Enzyme Defects

- Lactic acidosis can occur due to a variety of inherited defects in enzymes involved in glycogen storage diseases, gluconeogenesis, citric acid cycle (pyruvate oxidation), and electron transport (complex I deficiency; complex I, III, and IV deficiencies; and complex I and IV deficiencies). These are inborn errors associated with "primary" lactic acidosis.
- Disorders associated with "secondary" lactic acidosis include organic acidurias (propionic acidemia, methylmalonic acidemia, etc.), defects in fatty acid oxidation, and urea cycle enzymes.
- Acquired enzyme defects are related to thiamine deficiency (↓ pyruvate dehydrogenase complex activity) and biotin deficiency (↓ pyruvate decarboxylase activity).
- Infants and children are affected the most from inherited defects of enzymes.
- Clinical assessment of skeletal muscle, heart, hepatic, and neurologic functions helps in assessing the enzyme defect.
- Lactate measurement in plasma and CSF and enzyme determinations in cultured fibroblasts, lymphocytes, and muscle biopsies will help in making the final diagnosis.
- Treatment is generally unsatisfactory. Therapies that enhance lactate metabolism are of some help.

Diagnosis

- No unique clinical symptoms and signs can be attributable to lactic acidosis.
- Instead conditions such as shock and other tissue hypoxic conditions with high AG (>25–30) metabolic acidosis should suggest the presence of lactic acidosis.
- Lactate levels 5–10 mmol/L may not give a high AG acidosis at onset of hypoxic condition, but follow-up lactate levels are indicated.
- $\Delta AG/\Delta HCO_3^-$ of 1.6 is suggestive of lactic acidosis, because lactate anions are buffered by non-HCO_3^- buffers (mostly bone and proteins) sparing HCO_3^-/CO_2

buffer system. Note that this ratio does not always suggest the coexistence of metabolic alkalosis.

- The following laboratory results are unique to lactic acidosis:

1. Hyperuricemia: lactate competes with urate secretion in the proximal tubule
2. Hyperphosphatemia: cellular phosphate efflux due to hypoxia and unreplenished ATP hydrolysis
3. Leukocytosis: demargination of white blood cells due to epinephrine release
4. Normokalemia: lack of electrical gradient establishment due to lactate permeation into the cell. Therefore, K^+ exit from ICF to ECF does not occur

Treatment

Generally, patients with severe lactic acidosis are hemodynamically unstable and require close monitoring. Oxygen saturation, hemoglobin, and lactate levels need to be monitored closely. Also, blood pressure and volume status should be followed for hemodynamic status. Frequent assessment of ABG is necessary for proper management of lactic acidosis. Try to maintain blood pH $\geq$7.20. The main concern of acidosis is myocardial dysfunction. When arterial pH is <7.30, myocardial contractility is maintained by catecholamine stimulation. However, this effect is lost when pH is <7.10. For this reason, arterial pH needs to be maintained $\geq$7.20.

The following guidelines help manage a patient with lactic acidosis:

- Removing or treating the underlying cause improves lactic acidosis. However, it is not that simple to eliminate the cause, particularly in critically ill patients.
- As mentioned above, circulatory support is essential.
- Broad-spectrum antibiotic administration for sepsis is extremely important for SIRS/sepsis syndrome with circulatory support.
- Alkali treatment of metabolic acidosis is important; however, there are several disadvantages with this treatment (Table 5.3).

Table 5.3 Intravenous alkali treatment for metabolic (lactic) acidosis

Alkali	Advantages	Disadvantages
$NaHCO_3$	Rapid effect, inexpensive, easy to administer	Hypertonicity, hypernatremia, ↑ CO_2 production, ↑ intracellular acidosis, volume overload, no survival benefit
THAM	No increase in CO_2, penetrates cells to buffer intracellular pH, useful in the treatment of mixed metabolic and respiratory acidosis	Respiratory depression, hypoglycemia, hyperkalemia, liver necrosis in children. Avoid in renal failure
Carbicarb	A mixture of 0.33 M Na_2CO_3 and 0.33 M $NaHCO_3$, less CO_2 production	Same as $NaHCO_3$, no clinical benefit and nonavailability

$NaHCO_3$ Requirements

- Decide how much serum [HCO_3^-] you need to raise, i.e., ΔHCO_3^-.
- Estimate HCO_3^- space as 50% of body weight (kg) in metabolic acidosis. Some authors calculate as 40% (note that HCO_3^- space or deficit increases with an increase in [H^+] or a decrease in pH).
- Calculate the amount of $NaHCO_3$ that is needed to raise serum [HCO_3^-] to the desired level.

Example:

$$\text{Serum}\left[HCO_3^-\right] = 10 \text{ mEq/L}$$

$$\text{Desired serum}\left[HCO_3^-\right] = 15 \text{ mEq/L}$$

$$\Delta HCO_3^- = 5 \text{ mEq/L}$$

$$HCO_3^- \text{ space in a } 70\,\text{kg patient} = 70 \times 0.5 = 35\text{L}$$

$$\text{Amount of } NaHCO_3 \text{ required} = 35 \times 5 = 175\text{mEq}$$

- These calculations should be based on an ongoing pathologic process that is causing metabolic acidosis.
- Administer slowly as an isotonic solution at a rate of ~0.1 mEq/kg/min.
- Consider administration of calcium gluconate separately to prevent fall in ionized Ca^{2+} after alkali administration to improve cardiac function.
- Disadvantages of $NaHCO_3$ administration are shown in Table 5.3. However, one important advantage of $NaHCO_3$ administration is that it replaces buffering of lactate by proteins, particularly in the heart and brain. This buffering by $NaHCO_3$ administration restores the functions of proteins in these organs.
- It was also shown that CO_2 produced by $NaHCO_3$ administration does not cause intracellular acidosis in those patients with normal lung function compared to those with abnormal lung function.

THAM (Tris-Hydroxymethyl Aminomethane) Requirements

- THAM is an amino alcohol.
- It buffers H^+ by virtue of its NH_3 moiety in the urine. Therefore, its use is limited only to those with GFR >30 mL/min.
- It does not increase CO_2.
- Improves cardiac contractility.
- THAM is given as a 0.3 M solution (300 mEq/L), and its requirements for initial dose are calculated for the above example as:

$$\text{mL of } 0.3\,\text{M solution required} = \text{Body weight} \times \text{Base deficit}\left(HCO_3^-\right) 70 \times 5 = 350\,\text{mL}$$

- Continue THAM until blood pH >7.20.

Tribonat

- A buffering agent available in Europe.
- It is a mixture of THAM, $NaHCO_3$, acetate, and phosphate.
- Seems to generate less CO_2 and without much effect on intracellular pH.
- Not used in the USA.

Renal Replacement Therapies

- Intermittent hemodialysis is another mode of alkali administration.
- It has been used to avoid $NaHCO_3$-induced hyperosmolality and volume overload.
- Continuous renal replacement therapies (continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) with $NaHCO_3$ replacement fluid) were found to be efficacious in improving lactic acidosis (type A) in hemodynamically unstable patients and in type B acidosis due to metformin and other agents.

Thiamine and Riboflavin

- Thiamine is a cofactor for PDC, and activation of PDC may improve lactate levels.
- Riboflavin may provide FAD (flavin adenine dinucleotide), which is required in electron transport system.
- Both of these do not cause any adverse effects, and their use is optional.

Insulin

- Insulin increases the activity of PDC, and its use is beneficial in some patients with mild to moderate hyperglycemia.

Dichloroacetate

- Stimulates PDC and enhances pyruvate oxidation.
- Reduces lactate levels, improves pH, and raises serum [HCO_3^-].

- Despite its beneficial effects on lactic acidemia, there was no survival benefit, therefore not used routinely.
- However, it is effective in some patients with lactic acidosis due to inherited enzyme defects.

Inhibitors of Na/H Exchanger

- In hypoxic conditions with lactic acidosis, there is activation of myocardial Na/H exchanger. As a result, there is accumulation of excess intracellular Na^+ and Ca^{2+}, causing cardiac dysfunction. Inhibitors of Na/H exchanger (sabiporide, cariporide) alone or in combination with $NaHCO_3$ improved cardiac function and mortality in animals and one human study. Routine use of these inhibitors awaits further studies.

Vasodilators

- Nitroprusside therapy has been suggested for lactic acidosis. The rationale is that it causes vasodilation of the arterioles and promotes lactate metabolism. However, this therapy may not be recommended routinely in those patients with severe hypotension.

Methylene Blue

- Methylene blue is an oxidizing agent and thus acts like NAD. As a result, lactate is converted into pyruvate. Although i.v. methylene blue lowers lactate levels, it had no survival benefit.

D-Lactic Acidosis

- As shown in Fig. 5.1, D-lactate is the stereoisomer of L-lactate, and not a major product like L-lactate in normal subjects. Only a small amount of D-lactate is generated endogenously by methylglyoxal pathway and is oxidized to pyruvate. Small amount of D-lactate is excreted by the kidneys. Therefore, D-lactic acidosis is not seen in healthy humans. Exogenous sources of D-lactate include diet and foods such as yogurt, sour milk, tomatoes, apples, pickles, and bacterial fermentation of undigested carbohydrates in the colon. Other sources include ingestion of beer, wine, and propylene glycol and administration of Ringer's

lactate. Production of D-lactate and associated acidosis is seen mostly in ruminants such as cows. D-lactic acidosis in a patient with short bowel syndrome (SBS) was first described in 1979. Since then a number of cases both in children and adults have been reported. Risk factors, clinical manifestations, and management of D-lactic acidosis are described briefly in the following sections.

Conditions Associated with Risk for D-Lactate Toxicity in Humans

1. High risk: (1) short bowel syndrome (SBS), (2) intestinal bypass surgery, and (3) prolonged antibiotic use
2. Lower risk: (1) diabetic ketoacidosis, (2) propylene glycol use, (3) renal failure, (4) chronic pancreatic insufficiency, and (5) thiamine deficiency

Clinical Manifestations

- The most important clinical manifestations of D-lactic acidosis are related to central nervous system (CNS). Initially, these manifestations were described in patients with SBS. Patients usually present with confusion, slurred speech, ataxia, memory loss, irritability, abusiveness, headache, blurred vision, and nystagmus. In the original series, encephalopathy has been described in 100% of patients. In addition to CNS manifestations, a high AG metabolic acidosis with normal L-lactate levels should alert the physician for the possibility of D-lactic acidosis. The neurologic manifestations can last from hours to days.

Diagnosis

- As stated above, diagnosis of D-lactic acidosis is made on clinical manifestations and high AG metabolic acidosis. L-lactate levels are normal. Generally, d-lactate is not detected by the standard method of l-lactate determination. When diagnosis of D-lactic acidosis is made, blood should be sent to a special laboratory for D-lactate measurement, as the detection requires D-lactate dehydrogenase
- At times, the AG may be normal, and only hyperchloremic metabolic acidosis is present. This is due to increased excretion of D-lactate with Na^+ or K^+ rather than with NH_4^+ in the urine, resulting in decreased extracellular volume. At the same time, Cl^- is retained. Both volume loss and retention of Cl^- result in non-AG hyperchloremic metabolic acidosis. Because NH_4^+ is not excreted, the urinary AG is positive, suggesting the incorrect diagnosis of renal tubular acidosis

Pathogenesis

- Encephalopathy: The pathogenesis of D-lactic acidosis causing neurologic manifestations, particularly encephalopathy, is not clear. Initial studies have implicated D-lactate as a direct neurotoxin because it crosses the blood–brain barrier and affects brain function. Another support that D-lactate is a neurotoxin stems from observations that other forms of acidosis, including L-lactic acidosis, do not cause severe neurologic manifestations. However, administration of D-lactate via i.v. or oral to healthy volunteers did not elicit severe neurologic manifestations despite high circulating levels of D-lactate. This suggests that there is correlation between symptoms and D-lactate levels. Other studies have postulated that organic acids formed in the colon during fermentation, such as aldehydes, mercaptans, amines, and alcohols, might be neurotoxic and responsible for neurologic manifestations.
- Small bowel syndrome (SBS): The pathogenesis of neurologic manifestations due to SBS is clearly understood. Patients who have bowel length < 150 cm usually develop severe acidosis. Because of small bowl size, both digestion and absorption of carbohydrates are not complete; therefore, undigested or partially digested carbohydrates reach the colon where they undergo fermentation with production of organic acids. These acids lower the colon luminal pH and promote acid-resistant bacteria such as Lactobacillus acidophilus, Lactobacillus fermenti, Streptococcus bovis, and Bifidobacterium as well as Eubacterium species. These bacteria possess D-lactate dehydrogenase and produce D-lactate, which causes neurologic manifestations.

Treatment

Treatment includes (1) identification of risk factors and their correction to prevent acidosis and its consequences and (2) long-term management.

Acute Toxicity

- Use NaHCO3, as suggested for L-lactic acidosis.
- Provide adequate hydration. Avoid Ringer's lactate, as it may contain D-lactate.
- Correct precipitating factors such as avoidance of high carbohydrate diet. Provide low and simple carbohydrate diet. Parenteral carbohydrates can be given with thiamine in acute situations.
- Correct thiamine deficiency, if any.
- Avoid drugs that contain propylene glycol.
- Hemodialysis or other renal replacement therapies can remove D-lactate levels in acute situations such as encephalopathy.
- Use probiotics carefully because they may contain D-lactate-producing species. In fact, a case report suggests the association between probiotic use and D-lactate encephalopathy.
- Start antimicrobial therapy. Duration of therapy has not been established, but 7–14-day therapy is recommended until symptoms improve. Appropriate

antibiotics are oral vancomycin (125–500 mg 1–4 times/day), metronidazole (500 mg 3 times/day), ciprofloxacin (500 mg 2 times/day), amoxicillin (500 mg 2 times/day), and rifamixin (550 mg 2–3 times/day).

- Avoid neomycin and trimethoprim-sulfamethoxazole, as they may be associated with episodes of D-lactate encephalopathy.

Long-Term Management

- Once acute toxicity is controlled, measures to prevent future episodes of neurologic manifestations should be considered. These include the following: (1) low carbohydrate diet; (2) maintain adequate hydration, as malabsorption patients may develop dehydration; (3) correct thiamine deficiency; (4) avoid large quantities of alcohol or sugar-containing drinks; (5) limit intake of vegetables that contain oxalate, as oxalate can inhibit the enzyme D-2 hydroxy-acid dehydrogenase, which converts D-lactate into pyruvate; (6) encourage calcium supplements, up to 1 g/day, as calcium may increase the pH in the bowel that may prevent D-lactate production; and (7) long-term use of antibiotics may be considered on individual basis for repeated episodes of D-lactic acidosis.

Study Questions

Case 1 A 60-year-old man is admitted for a 2-week history of cyclic fever, weight loss of 10 lb., nausea, vomiting, and night sweats. He is not on any medications, and he has not seen a physician in years. Physical examination is normal except for a blood pressure of 100/40 mmHg and a pulse rate of 102 beats per minute. There is no lymphadenopathy. He weighs 74 kg. Pertinent laboratory results are as follows:

Serum	ABG
Na^+ = 142 mEq/L	pH = 7.20
K^+ = 4.2 mEq/L	pCO_2 = 20 mmHg
Cl^- = 104 mEq/L	pO_2 = 92 mmHg
HCO_3^- = 8 mEq/L	HCO_3^- = 7 mEq/L
BUN = 32 mg/dL	
Creatinine = 1.8 mg/dL	
Glucose = 64 mg/dL	
Uric acid = 9.4 mg/dL	
Measured serum osmolality = 312 mOsm/kg H_2O	
Alanine aminotransferase = 60 U/L (normal <38 U/L)	
Aspartate aminotransferase = 58 U/L (normal <41 U/L)	
Lactate dehydrogenase = 690 U/L (normal 115–221 U/L)	
White cell count = $8.2 \times 10^3/mm^3$	

Question 1 What is the acid–base disturbance?

Answer Based on the pH, serum [HCO_3^-], and AG of 30, the primary acid–base disorder is a high AG metabolic acidosis with appropriate respiratory response.

Question 2 Based on the osmolal gap of 14, do you suspect any alcohol intoxication?

Answer No. There are no clinical manifestations that are attributable to toxic alcohol ingestion with such a high AG. The osmolal gap of 14 can be attributable to causes other than alcohols.

Question 3 What other pertinent laboratory tests you order at this time?

Answer Serum lactate and ketones are the appropriate laboratory tests at this time. Serum lactate levels were 14 mmol/L, and ketones were positive. Thus, there are 20 (ΔAG 20; observed AG − normal AG (30–10 = 20)) excess anions in this patient. Of the 20 excess anions, lactate accounts for 14, and the remaining anions are possibly from ketoacids (due to starvation) and sulfate and phosphate from renal failure.

Question 4 Based on clinical presentation and high lactate level, what other consults do you request now?

Answer Hematology/oncology consult is extremely important. The hematologist felt that a bone marrow biopsy is valuable in making the diagnosis in the presence of normal white cell count and lymph nodes. The biopsy revealed extranodal T-cell lymphoma, and the lactic acidosis was attributed to lymphoma.

The patient's condition deteriorates, and his pH drops from 7.20 to 7.00 and HCO_3^- from 8 to 6 mEq/L. You intend to start the patient on $NaHCO_3$ drip to raise his serum [HCO_3^-] from 6 to 10 mEq/L.

Question 5 How much $NaHCO_3$ does he need to reach serum [HCO_3^-] of 10 mEq/L?

Answer The HCO_3^- space has increased; therefore, the pH did not improve. The amount of $NaHCO_3$ needed can be calculated as follows:

$$\begin{aligned}
&\text{Patient s weight} && = 74\,\text{kg}\\
&HCO_3^- \text{ space} && = 60\ \%\\
&\Delta HCO_3^- && = 4(10-6)\\
&\text{Amount of } HCO_3^- \text{ needed} && = 74\times 0.6\times 4 = 178\,\text{mEq}
\end{aligned}$$

The patient received 180 mEq of $NaHCO_3$, thiamine, and riboflavin, but serum [HCO_3^-] did not change.

Question 6 What is your next approach to improve lactate?

Answer Continuous venovenous hemofiltration (CVVH) with $NaHCO_3$ replacement is a reasonable approach to improve lactic acid level and metabolic acidosis.

Case 2 A 28-year-old woman was brought to the Emergency Department for agitation and respiratory distress, requiring intubation. She required fentanyl and lorazepam for sedation. Renal function was normal. Two days later, she had a low serum [HCO3⁻] of 12 mEq/L, a drop of 10 mEq/L from baseline value. An ABG shows a high anion gap metabolic acidosis.

Which one of the following acids may have contributed to her anion gap metabolic acidosis?

A. Acetoacetate
B. Methanol
C. Ethylene glycol
D. Lactic acid
E. Hippuric acid

The answer is D. The patient received lorazepam probably at high doses for sedation. Propylene glycol (PG) is a diluent found in many intravenous and oral drugs, including lorazepam. PG is metabolized by alcohol and aldehyde dehydrogenases to lactic acid. Each milliliter of lorazepam injection contains 828 mg of PG. Thus, high doses of lorazepam administration result in high circulating levels of lactic acid. PG is water soluble and is removed by hemodialysis and also continuous venovenous hemofiltration. Thus, choice D is correct.

Case 3 Match the drug effects of lactic acid shown in column A with the mechanisms of action shown in column B.

Column A	Column B
A. Metformin	1. Inhibition of mitochondrial protein synthesis
B. Tenofovir	2. Uncoupling of oxidative phosphorylation
C. Linezolid	3. Inhibition of pyruvate dehydrogenase complex
D. Thiamine deficiency	4. Increase in NADH/NAD^+ ratio, inhibition of gluconeogenesis from lactate, inhibition of mitochondrial respiration
F. Propofol	

Answers A = 4; B = 1; C = 1; D = 3; E = 2

Case 4 A 40-year-old woman with history of short bowel surgery is seen for slurred speech, confusion, weakness, impaired motor coordination, and irritability. She likes ice cream and develops mild neurologic problems following large quantities of ice cream. She is not on any medications or special diets. ABG: pH 7.27, pCO_2 24 mmHg, and calculated HCO_3^- 16. Urine ketones are negative. Serum lactate levels are 1.5 mmol/L. Serum creatinine is normal. The anion gap is 20, but osmolal gap is normal.

Which one of the following is the MOST likely cause of acid–base disturbance in this patient?

A. L-Lactic acid
B. Pyroglutamic acid
C. D-Lactic acid
D. Methanol
E. Topiramate

The answer is C. Except for topiramate, all other causes generate high AG metabolic acidosis. Topiramate causes non-AG metabolic acidosis due to inhibition of carbonic anhydrase. Serum lactate is normal; therefore, lactic acidosis is excluded. Also, methanol intoxication is excluded based on normal osmolal gap. There is no history of medication (Tylenol or Tylenol-containing narcotics) or antibiotic use. Therefore, pyroglutamic acidosis is ruled out. Based on the surgical history, high carbohydrate intake, and neurologic manifestations, the most likely diagnosis is D-lactic acidosis. Thus, option C is correct.

Case 5 The above patient (case 4) is admitted for management of neurologic manifestations and high AG metabolic acidosis. Which one of the following medications will improve her clinical status?

A. Oral vancomycin
B. Metronidazole
C. Ciprofloxacin
D. Rifamixin
E. All of the above

The answer is E. All of the above medications are indicated in the treatment of D-lactic acidosis. Duration of antibiotic therapy has not been established, but 7–14-day therapy is recommended until symptoms improve. Appropriate antibiotics are oral vancomycin (125–500 mg 1–4 times/day), metronidazole (500 mg 3 times/day), ciprofloxacin (500 mg 2 times/day), and rifamixin (550 mg 2–3 times/day). Thus, answer E is correct.

Neomycin and trimethoprim-sulfamethoxazole should be avoided, as they may be associated with episodes of D-lactate encephalopathy.

Case 6 A 40-year-old man is admitted to the intensive care unit for fever, hypotension, and lactic acidosis. Which one of the following mechanisms causes lactate production other than hypotension in sepsis?

A. Increased gluconeogenesis
B. Whole-body glucose uptake by noninsulin mechanisms
C. Production of cytokines
D. Aerobic glycolysis
E. All of the above

The answer is E. Hypotension and hypoxia are important causes of lactate production in sepsis. In addition, other mechanisms have been implicated. During

sepsis, insulin resistance and increased gluconeogenesis occur. Also, whole-body glucose uptake by noninsulin mechanisms occurs with release of cytokines such as tumor necrosis factor α and interleukin 6. Insulin resistance, gluconeogenesis, and cytokine stimulation of glucose uptake promote glycolysis and production of lactate from pyruvate.

Hyperlactatemia may also be caused by aerobic (not related to hypoxia) glycolysis. For example, sepsis causes high circulating levels of epinephrine, which stimulates Na/K-ATPase of skeletal muscle membrane and causes increased aerobic glycolysis. Thus, a major portion of the increased lactate levels may be attributed to aerobic glycolysis. Thus, answer E is correct.

Suggested Reading

Adeva-Andany M, Lòpez-Ojè M, Funcasta-Calderò R, et al. Comprehensive review of lactate metabolism in human health. Mitochondrion. 2014;17:76–100.

Apodaca AA, Rakita RM. Linezolid-induced lactic acid. N Engl J Med. 2003;348:86–7.

Arenas-Pinto A, Grant AD, Edwards S, et al. Lactic acidosis in HIV infected patients: a systematic review of published cases. Sex Transm Infect. 2003;79:340–4.

Blohm E, Lai J, Neavyn M. Drug-induced hyperlactatemia. Clin Toxicol. 2017;55:869–78.

Calza L, Manfredi R, Chiodo F. Hyperlactatemia and lactic acidosis in HIV-infected patients receiving antiretroviral therapy. Clin Nutr. 2005;24:5–15.

Carlos J, Velez Q, Janech MG. A case of lactic acidosis induced by linezolid. Nat Rev Nephrol. 2010;6:236–42.

Carson J, Cerda J, Chae J-H, et al. Severe lactic acidosis associated with linezolid use in a patient with the mitochondrial DNA A27006G polymorphism. Pharmacotherapy. 2007;27:771–4.

DeFronzo R, Fleming GA, Chen K, et al. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016;65:20–9.

Ewaschuk JB, Naylor JM, Zello GA. D-lactate metabolism in human and ruminant metabolism. J Nutr. 2005;135:1619–25.

Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. J Intensive Care Med. 2005;20:255–71.

Fodale V, Monaca L. Propofol infusion syndrome. An overview of a perplexing disease. Drug Safety. 2006;31:293–303.

Foretz M, Gugas B, Bertrand L, et al. Metformin: from mechanisms of action to therapies. Cell Metab. 2014;20:953–66.

Garrabou G, Soriano A, Lopez S, et al. Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. Antimicrob Agents Chemother. 2007;51:962–87.

Gurukripa Kowlgi N, Chhabra L. D-lactic acidosis: an underrecognized complication of short bowl syndrome. Gastroenterol Res Pract. 2015;2015:476215, 8 pages

Vl H. Lactic acidosis. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 351–82.

Kang KP, Lee S, Kang SK. D-Lactic acidosis in humans: review of update. Electrolyte Blood Press. 2006;4:53–6.

Kraut JA, Madias NE. Lactic acidosis. N Engl J Med. 2014;371:2309–19.

Kraut JA, Madias NE. Lactic acidosis: current treatments and future directions. Am J Kidney Dis. 2016;68:473–82.

Laski ME, Wesson DE. Lactic acidosis. In: Acid-base and electrolyte disorders. A companion to Brenner & Rector's the Kidney. Philadelphia: Saunders; 2002. p. 83–107.

Levy B. Lactate and shock state: the metabolic view. Curr Opin Crit Care. 2006;12:315–21.

Mirrakimov AE, Voore P, Halytskyy O, et al. Propofol infusion syndrome in adults: a clinical update. Crit Care Res. 2015:260385, 10 pages

San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg effect. Carcinogenesis. 2017;38:119–33.

Soriano A, Mirò O, Mensa J. Mitochondrial toxicity associated with linezolid. N Engl J Med. 2005;353:2305–6.

Suetrong B, Walley KR. Lactic acidosis in sepsis: it's not all anaerobic. Implications for diagnosis and management. Chest. 2016;149:252–61.

Wang Y, Huang Y, Yang J, et al. Pyruvate is a perspective alkalizer to correct hypoxic lactic acidosis. Military Med Res. 2018;5:13.

Wu D, Kraut JA. Role of NHE1in the cellular dysfunction of acute metabolic acidosis. Am J Nephrol. 2014;40:26–42.

Chapter 6
Ketoacidosis

Ketones are acetone, acetoacetic acid (acetoacetate), and β-hydroxybutyric acid (BHB). Of these, only acetoacetate and BHB cause acidosis, whereas acetone does not cause acidosis. Acetone is formed by nonenzymatic decarboxylation of acetoacetate, and does not contribute any acid load to the body (Fig. 6.1). Clinically, metabolic acidosis due to ketone overload is caused by diabetes, alcohol, and starvation. Therefore, this chapter focuses on only diabetic, alcoholic, and starvation ketoacidosis.

Diabetic Ketoacidosis

In general, diabetic ketoacidosis (DKA) is the most common presentation in patients with type 1 diabetes. It is also common in patients with type 2 diabetes. DKA is an important acute cause of morbidity and mortality in these patients. Symptoms of DKA were observed before the discovery of insulin by Kussmaul as early as 1874.

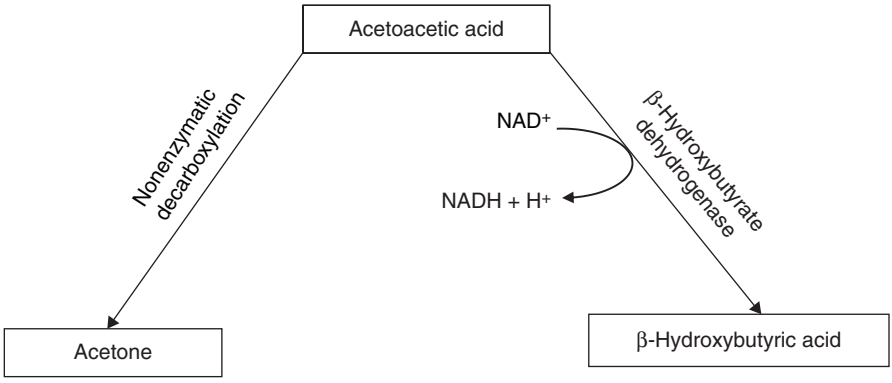

Fig. 6.1 Formation of acetone and β-hydroxybutyric acid from acetoacetate

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_6

An association between DKA and coma was established by the 1880s. After the discovery of insulin in 1922, deaths due to DKA have dramatically decreased from 60% to <2%. DKA is a condition that is characterized by hyperglycemia (>250 mg/dL), ketonemia, ketonuria, and high anion gap (AG) metabolic acidosis. Hyperglycemia causes hyperosmolality and glucosuria. Both glucosuria and ketonuria cause massive urinary losses of water, Na^+, K^+, and phosphate. As a result, severe volume depletion and electrolyte losses occur in DKA.

Pathogenesis of DKA

Hyperglycemia

DKA is produced due to absolute or relative deficiency of insulin with concomitant increase in hormones that oppose the action of insulin. These are called counter-regulatory hormones, which are glucagon, epinephrine, norepinephrine, cortisol, and growth hormone. Of these hormones, glucagon plays a major role in DKA. However, it should be noted that DKA does not generate without insulin deficiency or its resistance. Insulin deficiency and glucagon cause hyperglycemia by impaired peripheral glucose utilization, increased gluconeogenesis by the liver and kidney, and glycogenolysis. As stated above, hyperglycemia causes glucosuria with resultant volume depletion and prerenal azotemia.

Ketogenesis

Two organs are involved in ketogenesis: adipose tissue and liver. Insulin deficiency causes lipolysis. During lipolysis, free fatty acids (FFAs) are formed from triglycerides by hormone-sensitive lipase activity. Epinephrine stimulates this enzyme (Fig. 6.2). Once FFAs are formed in the adipocyte, they are released into the blood and transported to the liver. Long-chain fatty acids such as palmitic acid cannot enter the liver mitochondria where β-oxidation occurs to form ketones. Therefore, these long-chain FFAs need to be activated. This process of activation involves ATP, coenzyme A, and FFA to form an activated fatty acid or acyl-coenzyme A (acyl-CoA). This reaction is catalyzed by the enzyme acyl-CoA synthetase or thiokinase and occurs in the cytoplasm of hepatocyte. Acyl-CoA can enter the intermembrane space but cannot penetrate the inner mitochondrial membrane. Entrance into the inner mitochondrial membrane is facilitated by carnitine via transfer of acyl groups to carnitine to form acylcarnitine. This transfer is catalyzed by the enzyme carnitine palmitoyl transferase 1 (CPT1) present in the mitochondrial outer membrane. The acylcarnitine is then carried to the mitochondrial matrix by the inner membrane transporter carnitine/acylcarnitine translocase in exchange for carnitine. From acylcarnitine, acyl group is transferred to CoA to reform acyl-CoA, and carnitine is released. Carnitine is transported back to combine with acyl-CoA to form acylcarnitine for the cycle to continue. This transfer is facilitated by CPT2 located in the inner mitochondrial membrane.

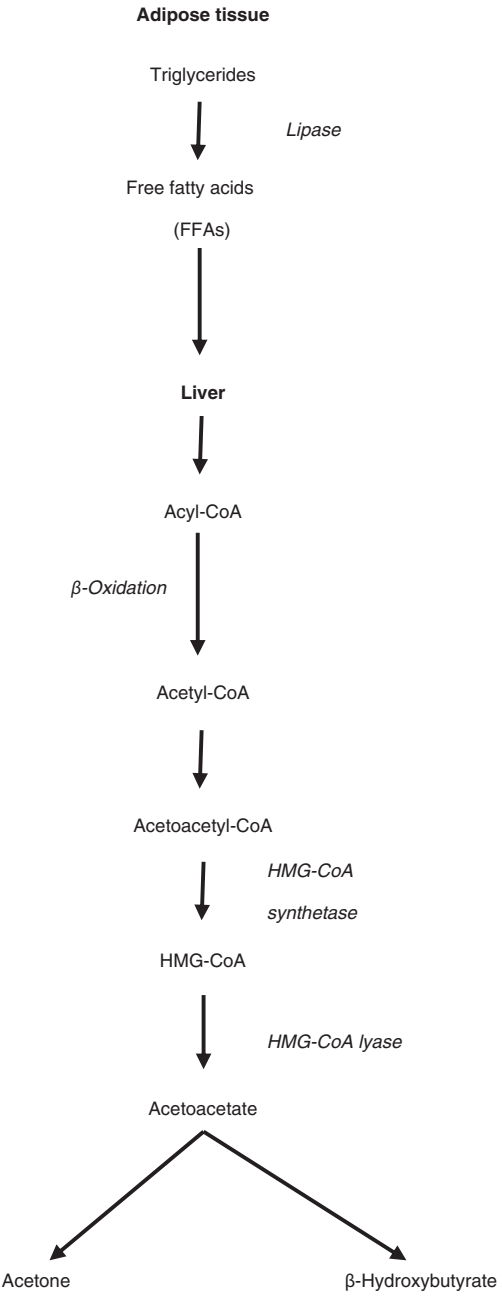

Fig. 6.2 Simplified diagram showing the formation of free fatty acids in the adipose tissue and ketones in the liver. HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A

Once acyl-CoA is in the mitochondrial matrix, it undergoes β-oxidation to yield acetyl-CoA. Two molecules of acetyl-CoA react to form acetoacetyl-CoA. Subsequently, another molecule of acetyl-CoA combines with acetoacetyl-CoA to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). This reaction is catalyzed by HMG-CoA synthetase. The HMG-CoA is further cleaved into aceto-

acetate and acetyl-CoA by HMG-CoA lyase. Acetoacetate is subsequently reduced to β-hydroxybutyrate by the enzyme β-hydroxybutyrate dehydrogenase. This reaction is controlled by high NADH/NAD^+ ratio (see Fig. 6.1). Among counterregulatory hormones, glucagon plays an important role in ketogenesis in diabetic patients. It has been reported that 1000–2000 mEq/L/day of ketones are formed in patients with severe diabetic ketoacidosis.

Ketogenesis is under the control of a substrate for fatty acid synthesis called malonyl-CoA. In fed state, fatty acid synthesis occurs because of high circulating levels of insulin. During this fatty acid synthesis, malonyl-CoA inhibits the enzyme CPT1. When insulin levels are deficient or low, the synthesis of malonyl-CoA decreases, and its level falls. As a result, the inhibitory effect of malonyl-CoA on CPT1 is removed. This facilitates the action of CPT1 so that acyl-CoA can combine with carnitine for entry into the mitochondrion. Thus, ketogenesis is regulated by malonyl-CoA.

In summary, ketones are formed in diabetes from elevated levels of FFAs released from triglycerides. Long-chain fatty acids must be activated before they enter liver mitochondria, where they undergo β-oxidation to form acetoacetate. Subsequently, acetoacetate is reduced to β-hydroxybutyrate. Also, acetoacetate undergoes spontaneous nonenzymatic decarboxylation to form acetone, which is removed by the lungs causing acetone breath in patients with DKA. The kidneys also excrete ketones until glomerular filtration rate (GFR) is decreased substantially.

Metabolic Acidosis

Metabolic acidosis results from excess production of acetoacetic acid and β-hydroxybutyric acid. Both these acids dissociate at body fluid pH to yield H^+, which are buffered by HCO_3^- ions. As a result, serum [HCO_3^-] decreases, and a high AG metabolic acidosis develops. In uncomplicated DKA, the increase in serum AG above normal approximates the decrease in serum HCO_3^- from normal levels of 24 mEq/L. In other words, the $\triangle$AG/$\triangle HCO_3^-$ ratio is 1:1.

In mild DKA, the body volume is relatively preserved due to intake of fluids by the patient because of thirst. If the patients drink fruit juice which contains citrate, depletion of serum HCO_3^- level may not decrease that much because of citrate conversion into HCO_3^-. This results in mild AG metabolic acidosis. Also, the kidneys play an important role in maintaining mild acidosis by excreting large quantities of ketones. However, when the patient develops severe volume depletion, excretion of ketones is diminished with resultant accumulation of these ketones in the serum and development of very high AG metabolic acidosis. In severe acidosis, the serum HCO_3^- level may diminish to as low as 5 mEq/L.

Besides ketones, the diabetic patients also generate other acids such as L-lactic acid. It was suggested that D-lactic acid also contributes to metabolic acidosis in DKA. Because of ketones, and L- as well as D-lactic acids, the patients develop a very high AG metabolic acidosis at presentation of severe DKA.

Ketonemia and Ketonuria

As stated above, ketones are generated and excreted by the kidneys until GFR is substantially reduced. In DKA, production of β-hydroxybutyrate is more than the production of acetoacetate. As stated above, the ketones are excreted if volume depletion is mild and GFR is near normal. Under these conditions, ketonemia is less than ketonuria. When volume depletion is severe and GFR is substantially decreased, excretion of ketones is decreased, and ketonemia predominates ketonuria.

Precipitating Factors

Several epidemiologic studies have shown that noncompliance or poor adherence to insulin regimen is the most common precipitating factor for DKA in adults. However, infection (urinary tract infection, sepsis, pneumonia, etc.) seems to be the common cause for DKA worldwide. DKA is an initial manifestation of DKA more in children than in adults. Several other precipitating causes for DKA have been reported, as shown in Table 6.1.

Table 6.1 Precipitating factors for DKA

Factor	Comment
1. Noncompliance or poor adherence to insulin administration	Inadequate insulin initiates DKA
2. Infection	Urinary tract infection, septicemia, and other infections demand additional insulin requirements
3. First episode of DKA	Indicates new onset of type 1 diabetes mostly in children
4. Other factors Myocardial infarction Acute pancreatitis Stress Consumption of fluids with high sugar content Stroke Intestinal obstruction	All of these conditions cause insulin resistance or higher insulin dose requirements
5. Drugs Glucocorticoids Thiazide diuretics First and second generation antipsychotics	Raise glucose levels
6. Sodium-glucose cotransporter-2 inhibitors	These drugs cause “euglycemic DKA” (see further discussion)

Clinical Manifestations

History and physical examination, including precipitating factors of DKA, is extremely important. Initial presentation of patients with DKA is attributable to hyperglycemia such as polydipsia, polyuria, thirst, weight loss, nausea, and vomiting. Abdominal pain mimicking acute abdomen is also a common complaint, which is due to acidosis, and the pain is related to the severity of acidosis. This complaint should be differentiated from diabetic gastroparesis which does not improve after correction of acidosis, whereas abdominal pain does improve following correction of acidosis.

Signs include tachycardia, tachypnea, Kussmaul breathing (deep and frequent breathing), hypothermia, hypotension, and altered mental status. Stupor and coma are seen mostly in children. Altered mental status is usually attributed to acidosis and hyperosmolality.

On physical examination, the patients look ill and volume depleted. Acetone breath (fruity odor) is common. Hypotension with orthostatic blood pressure and orthostatic pulse changes suggest severe volume depletion.

Laboratory Findings

By definition, DKA is a triad of hyperglycemia, metabolic acidosis, and ketonemia as well as ketonuria. The initial laboratory tests should include complete blood count, serum electrolytes, glucose, creatinine, BUN, Ca^{2+}, Mg^{2+}, phosphate, total protein, albumin, ketones, and osmolality. Urinalysis that includes ketones should be obtained. ABG is needed in patients with very low HCO_3^- levels and hypoxia. Venous ABG may be sufficient in patients with mild-moderate DKA and normal mentation. AG should always be calculated. Serum needs to be diluted for ketones for appropriate testing. Determination of β-hydroxybutyrate by an analyzer is appropriate in severe ketosis. Common laboratory findings are shown in Table 6.2.

Based on the above laboratory findings, the severity of DKA is classified into mild, moderate, and severe forms. The criteria for this classification are shown in Table 6.3.

Treatment

In the Emergency Department, correct diagnosis of DKA is important. Once diagnosis is established, close monitoring of vital signs, oxygenation, and hemodynamic status is also extremely important. The goals of DKA management include:

1. Correction of volume deficit
2. Correction of electrolyte deficit

Table 6.2 Laboratory findings in DKA

Lab value	Commonly observed value	Comment
WBC	Elevated up to 15 to 17000	Due to stress, demargination, and elevated levels of cortisol and catecholamines
Hgb, hematocrit	Elevated	Due to volume depletion
Serum glucose	>250 mg/dL	Insulin deficiency/resistance
Serum HCO_3^-	<20 mEq/L	Low because of buffering ketone anions
Serum and urine ketones	Positive	Reagent strips (Ketostix, Acetest) contain nitroprusside, which reacts with acetoacetate and acetone but not with β-hydroxybutyrate
Serum Na^+	Usually <140 mEq/L	Depletion of body stores and due to high glucose levels
Serum K^+	Usually >5.2 mEq/L	Due to volume depletion and movement from ICF to ECF compartment
Serum Cl^-	Usually normal	Depletion of body stores common
Serum creatinine and BUN	Elevated	Due to volume depletion. Note that acetoacetate may falsely elevate creatinine levels
Serum Ca^{2+} and Mg^{2+}	Usually low unless volume depleted	Mild depletion of body stores
Serum phosphate	Usually low unless volume depleted	Severe depletion of body stores

Table 6.3 Diagnostic criteria for DKA

Lab value	Mild	Moderate	Severe
Serum glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25–7.30	7.00–7.24	<7.00
Serum HCO_3^- (mEq/L)	15–18	10–15	<10
Anion gap	>10	>12	>12
Serum ketones	Positive	Positive	Positive
Urine ketones	Positive	Positive	Positive
Mental status	Alert	Alert-drowsy	Stupor

3. Correction of hyperglycemia and acidosis
4. Avoid complications of treatment
5. Identification and treatment of precipitating factors

Correction of Volume Deficit

Patients with DKA lose water from both extracellular and intracellular compartments. Generally it is difficult to estimate the exact percentage of water loss; however, several studies have shown a range of loss, which is usually expressed as loss

Table 6.4 Approximate deficits of water and electrolytes per kg and total loss in a 70 kg patient with DKA

	Range	Total loss (range)
Water (mL/kg)	30–100	2–7 L
Na (mEq/kg)	7–10	490–700
K^+ (mEq/kg)	3–5	210–350
Cl^-(mEq/kg)	3–9	210–630
Phosphate (mg/kg)[a]	15–21	1050–1470
Ca^{2+} (mEq/kg)	1–2	70–140
Mg^{2+} (mEq/kg)	1–2	70–140

[a]Commonly reported in mmol/kg. To obtain mmol from mg multiply by 0.32

in mL/kg body weight. Table 6.4 shows not only water but also electrolyte losses in DKA. A representative total loss in a 70 kg patient is also shown in the table.

It is generally agreed that the most important initial therapeutic measure in DKA is appropriate replacement of volume to improve blood pressure, pulse rate, and urine output. As shown in Table 6.4, a 70 kg patient may lose up to 7 L of fluid, and replacement is needed. The recommended initial fluid of choice is *normal* (*0.9%*) *saline*. One liter of saline should be given in the first 1 h, followed by another liter during the second hour. Infusion of normal saline should be continued until:

A. Volume status is improved
B. Na^+ loss is replenished
C. Urine output is adequate

Adequate volume repletion accomplishes the above three objectives so that hemodynamic stability is established. Kidney function improves with volume expansion. However, it is extremely important to follow electrolytes as changes may occur in these electrolytes once urine output is adequate. Avoid rapid expansion of volume to prevent cerebral edema.

Correction of Electrolyte Deficit

Na^+ Serum Na^+ level at the time of admission is usually low because of water movement from intracellular to the extracellular compartment caused by hyperglycemia-induced hyperosmolality. For each 100 mg/dL above normal serum glucose level (90–100 mg/dL), serum Na^+ level decreases by 1.6 mEq/dL from normal level of 140 mEq/L. At times, even after correction of Na^+ for hyperglycemia, the serum Na^+ level may remain low because of osmotic diuresis and loss of Na^+ with ketones in the urine. As shown in Table 6.3, 7–10 mEq/L/kg of Na^+ loss occurs in DKA. Occasionally hypernatremia is seen on admission. This indicates severe volume depletion, and vigorous volume replacement with normal saline is required. It should be remembered that normal saline is relatively hypotonic in a hypernatremic patient. Irrespective of serum Na^+ concentration on admission, infusion of normal saline improves not only volume status but also total body Na^+ content.

K^+ On presentation, serum K^+ is usually high. The reported K^+ by several studies ranges from 5.3 to 5.6 mEq/L. Hyperkalemia is related to (1) insulin deficiency; (2) shift from intracellular to extracellular movement with water (solvent drag); and (3) severe volume depletion. Despite hyperkalemia, there is a total body loss of 210–350 mEq of K^+, which is due to osmotic diuresis as well as loss with ketones. During volume replacement with normal saline, hypokalemia is usually observed, and replacement is necessary. Initially 20 mEq/Lin the form of KCl may be started with volume expansion. Subsequently, the dose may be increased to 40 mEq/L when renal function is normal. At times, a combination of KCl and potassium phosphate may be used to improve both K^+ and phosphate. The dose of KCl may increase once insulin is started.

Phosphate Serum phosphate concentration is usually low on admission due to osmotic diauresis. Approximately 1–1.5 g (320–480 mmol) of phosphate is lost in DKA. Loss of phosphate is rather common from intracellular stores. Replacement of phosphate as potassium phosphate (K Phos) is needed once volume is expanded and insulin is started. Note that both K^+ and phosphate are transported to the intracellular compartment by insulin. One of the complications of phosphate administration is hypocalcemia, and frequent measurement of serum Ca^{2+} levels is needed.

Hypocalcemia and hypomagnesemia become evident once volume is replaced and should be corrected with appropriate supplements.

Correction of Hyperglycemia and Acidosis

Volume expansion with normal saline lowers blood glucose levels substantially. However, acidosis and AG will not improve. Therefore, insulin should be administered to improve hyperglycemia, metabolic acidosis, cellular functions, and suppress ketogenesis. The recommended dose is 0.1 U/kg/h of regular insulin intravenously (iv) until glucose levels reach 200–250 mg/dL and HCO_3^- levels are above 15 mEq/L. The rate of decrease in blood glucose levels should be approximately 50 mg/h until the levels reach 200–250 mg/dL. The improvement of serum HCO_3^- concentration is due to conversion of ketones into HCO_3^-. Infusion of $NaHCO_3$ is not indicated unless the pH is <6.9 and cardiac contractility (output) is decreased. Controlled trials have shown no benefit from $NaHCO_3$ administration. In addition, paradoxical CNS acidosis has been reported with $NaHCO_3$ administration. Therefore, judicious use of bicarbonate administration is suggested.

Insulin therapy should be held if serum K^+ level is <3.4 mEq/L. Once insulin is started after correction of hypokalemia, i.v. KCl should be continued until DKA is resolved. Also, i.v. fluids should be switched to D5W and 0.45% saline once blood glucose levels reach 200–250 mg/dL. Occasionally, 10% dextrose can be used for severe hypoglycemia. If the patient recovers from DKA and is stable, oral intake of food should be encouraged. Metabolism of both food and i.v. glucose will improve

Table 6.5 Complications of DKA treatment

Complication	Comment
Hypokalemia	Due to volume expansion, insulin therapy, and at times $NaHCO_3$ therapy
Hypoglycemia	Insulin therapy
Hypophosphatemia	Due to volume expansion and insulin therapy
Hyperchloremic metabolic acidosis	Hyperchloremic metabolic acidosis does develop in some patients in the recovery phase of DKA because the regeneration of HCO_3^- from ketones is decreased due to loss of excess ketones in the urine prior to hospitalization. Also, administration of fluids that contain high chloride may contribute to this type of transient acidosis
Cerebral edema	Rare but common in children. Headache, low heart rate, lethargy, and neurologic deterioration are the initial manifestations of cerebral edema. Preventive measures include gradual replacement of volume to avoid a rapid fall in plasma osmolality and prevent hypoglycemia. Symptomatic treatment includes mannitol or 3% NaCl administration. An MRI of the brain after signs and symptoms improve may be helpful

HCO_3^- concentration, and thus metabolic acidosis. Once DKA has resolved, which takes 24–48 h, subcutaneous (s.c.) long- or intermediate-acting insulin should be started along with s.c. regular insulin, and the patient can be transferred out of the intensive care unit. At this time, i.v. fluids should be discontinued, and oral intake of fluids should be encouraged.

Insulin stimulates Na/H exchanger in brain cells. This stimulation causes extrusion of H^+ from the cell in exchange for Na^+ into the cells. Water follows Na^+. Overzealous volume expansion and insulin administration immediately after diagnosis may place the patient at risk for cerebral edema. Therefore, insulin administration should be delayed for 1–2 h after starting fluid therapy. This delay in insulin therapy would avoid a sudden fall in plasma effective osmolality.

Avoid Complications of Treatment

Treatment of DKA is not without any complications. Reported complications are shown in Table 6.5.

Identification and Treatment of Precipitating Factors

A detailed history of precipitating factors for DKA (see Table 6.1) is extremely important. A WBC count >25,000 even in the absence of fever may indicate infection and warrants initiation of antibiotics pending culture results. Appropriate management of other risk factors is also warranted.

Euglycemic DKA

Euglycemic DKA is a newly described complication of sodium-glucose cotransporter-2 (SGLT-2) inhibitors such as canagliflozin. These are newly introduced oral hypoglycemic agents, which inhibit glucose absorption in the proximal tubule. As a result, the patient loses glucose in the urine. These inhibitors lower serum glucose levels in type 2 and in combination with insulin in type 1 diabetic patients. However, SGLT-2 inhibitors have been shown to cause DKA with normal or slightly elevated glucose levels, and the condition is called *euglycemic DKA*. The risk of DKA is much higher in type 1 than in type 2 diabetic patients. Although the frequency of euglycemic DKA is rather rare, some patients may require hospitalization. Relative lack of insulin and infections seem to precipitate DKA. Potential mechanisms include failure to suppress lipolysis and ketogenesis by low levels of insulin in combination with elevated levels of glucagon. Also, decreased excretion of ketones by the kidneys seems to precipitate DKA.

This term euglycemic DKA may not be appropriate because some of the patients had hyperglycemia. Irrespective of glucose levels, all patients have signs and symptoms of classical DKA (see Symptoms and Signs of DKA). Treatment includes discontinuation of SGLT-2 inhibitors and appropriate use of insulin.

Hyperglycemic Hyperosmolar State

Hyperglycemic hyperosmolar state (HHS) is sometimes confused with DKA. In contrast to DKA, most of the patients with HHS are adults (elderly) with type 2 diabetes. Very few children present with HHS. Volume depletion is severe compared to DKA.

Definition HHS is characterized by the following:

1. Severe hyperglycemia (>600 mg/dL) with hyperosmolality (>320 mOsm/kg H_2O)
2. Dehydration
3. Absence of significant ketoacidosis

Laboratory findings Urine and serum ketones are small, and measured β-hydroxybutyrate levels are <3 mmol/L (31 mg/dL). In DKA, serum or urine β-hydroxybutyrate levels are >3 mmol/L. Arterial pH is usually >7.30, and serum HCO_3^- is >18 mEq/L. AG is slightly elevated. Creatinine and BUN are markedly elevated.

Clinical manifestations Polyuria and polydipsia start much earlier than depressed sensorium because of hyperglycemia. Altered mental status includes confusion, disorientation, obtundation, and finally coma when effective serum osmolality is

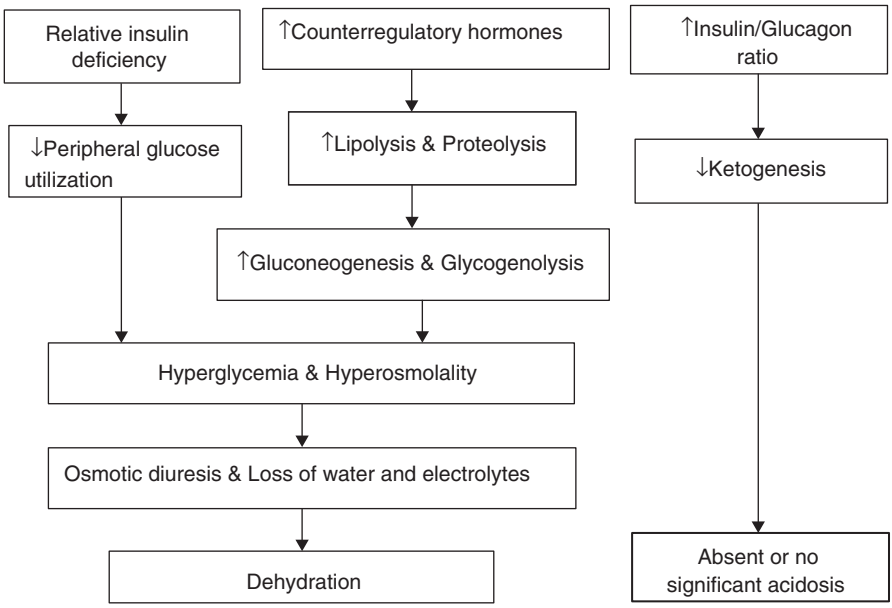

Fig. 6.3 Pathogenesis of hyperglycemic hyperosmolar state

>340 mOsm/kg H_2O. In contrast, patients with DKA do not usually present with this much of effective osmolality. The depressed sensorium is rather common in elderly patients. Animal studies have shown that water loss from CNS due to hyperglycemia may cause brain shrinkage initially followed by recovery of brain volume in 4–6 h. Severe volume depletion and hemodynamic instability are common similar to DKA.

Pathogenesis The pathogenesis of HHS is similar to DKA: relative insulin deficiency with elevated counterregulatory hormones. Hyperglycemia is related to poor peripheral glucose utilization and increased gluconeogenesis and glycogenolysis. The resulting hyperglycemia causes osmotic diuresis, leading to water and electrolyte losses (Fig. 6.3).

There are few observations to account for the absence of ketoacidosis in HHS. It was suggested that there is sufficient insulin (relative insulin deficiency) to inhibit lipolysis but not enough to stimulate peripheral glucose uptake. Unlike in DKA, insulin/glucagon ratio is high that is adequate to inhibit ketogenesis. Another explanation for absence of ketosis is relative hepatic resistance to glucagon in combination with mild decrease in malonyl-CoA levels. As mentioned previously, malonyl-CoA inhibits CPT1 enzyme, and this enzyme is responsible for transport of activated FFAs to enter the mitochondria for oxidation and ketogenesis.

Precipitating factors The most common precipitating factor for HHS is infection. Pneumonia and urinary tract infections are dominant infections because the patients

are elderly with type 2 diabetes. Other precipitating factors are comorbidities such as stroke, myocardial infarction, trauma, poor water intake, and medications, as documented under DKA.

Treatment The management of HHS is in many aspects similar to the treatment of DKA. It includes (1) volume repletion; (2) insulin administration; (3) correction of electrolyte deficits; and (4) identification and treatment of precipitating factors.

Fluids Water loss is greater in HHS than in DKA because of severe hyperglycemia. Normal (0.9%) saline is the fluid of choice. Approximately 50% of volume loss can be replaced with normal saline in first 12 h, and the remaining 50% loss can be replaced with either normal, half (0.45%)-normal, or D5W/0.45% saline depending on serum glucose and electrolyte levels, urine output, and vital signs. Volume expansion alone can decrease serum glucose and osmolality substantially. In hypernatremic patients, lowering serum Na^+ level by 8–12 mEq/L/24 h is recommended.

Insulin Patients with HHS are more sensitive to insulin than patients with DKA. The indication for i.v. insulin administration is when serum osmolality stops declining with fluid administration. The recommended dose is 0.05–0.1 U/kg/h. The dose can be doubled if serum glucose is not falling by 50–70 mg/dL/h. It should be noted that insulin should not be started in a patient with serum K^+ levels <3.5 mEq/L. Once serum glucose levels reach 250–300 mg/dL, insulin dose should be reduced to below 0.05 U/kg/h. Insulin boluses are not recommended. The total requirements of insulin for patients with HHS are usually less than those patients with DKA.

Electrolytes As in DKA, deficits of K^+, phosphate, and Mg^{2+} are higher in HHS than in DKA. With improvement in renal function and urine output, the electrolyte deficits become severe without replacement. Higher rates of K^+ replacement are necessary after insulin administration. Therefore, frequent measurements of these electrolytes are necessary. It should be noted that hypokalemia and hypophosphatemia may precipitate rhabdomyolysis. $NaHCO_3$ administration is contraindicated.

Precipitating factors Identification and treatment of precipitating factors such as infection are indicated to improve HHS.

Other Patients with HHS are at risk for arterial and venous thromboembolism; therefore, prophylactic anticoagulation with low molecular weight heparin is suggested.

Alcoholic Ketoacidosis

The development of ketosis in nondiabetic alcoholics was first described in 1940, and the term *alcoholic ketoacidosis* (AKA) was introduced in 1970. Since then, a number of studies demonstrated AKA following abstinence of prolonged alcohol

abuse. Alcohol withdrawal also precipitates ketoacidosis due to catecholamine release**.** Starvation because of nausea and vomiting may cause insulin deficiency and lipolysis.

Pathogenesis of ketogenesis Ethanol and its metabolic products are toxins. Ethanol metabolism itself partially contributes to ketogenesis. Ethanol is initially metabolized to acetaldehyde. This reaction is catalyzed by the enzyme alcohol dehydrogenase. Acetaldehyde is further metabolized to acetate (acetic acid), and this conversion is facilitated by the enzyme acetaldehyde dehydrogenase. Both reactions require the reduction of NAD^+ to NADH + H^+ with resultant increase in the ratio of $NADH+H^+/NAD^+$. Acetate is further converted into acetoacetate, which becomes an important substrate for β-hydroxybutyrate (Fig. 6.4). Thus, ethanol itself contributes to ketoacidosis.

Another mechanism of ketogenesis from alcohol ingestion is through lipolysis, as shown in Fig. 6.2. Ethanol inhibits gluconeogenesis, depletes hepatic glycogen stores, and increases lipolysis. These effects of ethanol are caused by relative insulin deficiency, glucagon excess, and increase in catecholamines. Among ketoacids, the concentrations of β-hydroxybutyrate in AKA are much higher than in DKA. The conversion of NAD^+ to $NADH+H^+$ also enhances the production of lactate from pyruvate. In addition to ketoacidosis, alcoholics may develop lactic acidosis. The pathogenesis of AKA, thus, includes ethanol itself, starvation, insulin deficiency, excess glucagon, and catecholamines.

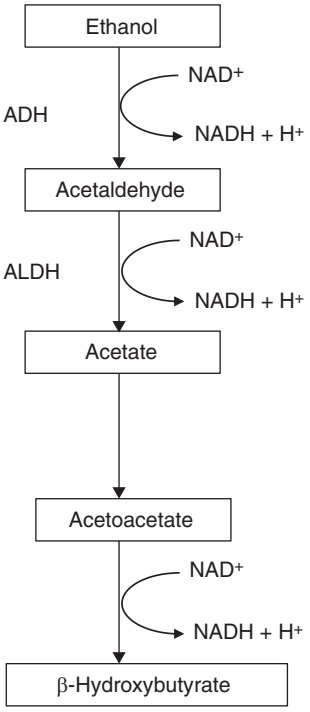

Fig. 6.4 Metabolism of ethanol. ADH alcohol dehydrogenase, ALDH acetaldehyde dehydrogenase

Clinical manifestations Most patients present with nausea, vomiting, and abdominal pain. Mental status may be normal or minimally affected despite severe acidosis. When the level of consciousness is severely affected, the diagnosis of severe hypoglycemia, sepsis, thiamine deficiency, or head trauma may be suspected. Alcohol withdrawal may present with confusion and abnormal behavior.

On physical examination, the patient may present with tachycardia, tachypnea, hypotension, and abdominal pain without ascites. Moderate to severe volume depletion is rather common. Hepatomegaly may be seen occasionally. Clinical or subclinical pancreatitis may be present.

Laboratory findings Most common laboratory features include:

1. Low or near-normal glucose levels—due to starvation and depleted liver glycogen stores
2. Elevated creatinine and BUN—due to volume depletion
3. Hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia are frequent in many patients. Low HCO_3^- level is common due to hyperventilation and metabolic acidosis
4. Slightly elevated lactic acid levels—due to conversion of pyruvate to lactate
5. High AG metabolic acidosis—due to ketoacids and lactic acid
6. Metabolic alkalosis—due to vomiting
7. Respiratory alkalosis—due to abdominal pain (a triple acid–base disorder is rather common in alcoholics)
8. Hyperchloremic metabolic acidosis—due to excess urinary loss of ketones and saline administration
9. Low or absent alcohol levels
10. Nitroprusside test gives weak reaction (mostly 1+) because of increased levels of β-hydroxybutyrate compared to acetoacetic acid
11. High osmolar gap can be seen occasionally because of ketones as well as some alcohol in some patients

Treatment consists of:

1. Correction of hypoglycemia by giving D5W (5% dextrose in water)
2. Correction of volume depletion by giving normal saline. This will also improve serum Na^+ level but raises Cl^- with resultant hyperchloremic metabolic acidosis
3. Correction of electrolyte deficits such as hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia
4. Correction of thiamine deficiency to prevent Wernicke's encephalopathy. Riboflavin is also recommended
5. No specific treatment for metabolic acidosis is needed, as infusion of glucose will correct not only plasma glucose but also ketone production. Glucose administration stimulates insulin release, which suppresses not only glucagon but ketogenesis as well

Hemodynamic stability is maintained by volume expansion. Volume expansion inhibits adrenergic surge and improves renal function. Replacement of electrolyte deficits is necessary during volume expansion. Gradual institution of dietary intake helps improve metabolic acid–base disorders. The amount of volume requirements such as D5W and normal saline should be individualized.

Starvation Ketoacidosis

The mechanisms for ketogenesis in starvation ketoacidosis are similar to those described for DKA. However, starvation ketoacidosis is mild and self-limited. With decrease in food intake, insulin secretion is decreased but that of glucagon increases with resultant production of ketone bodies. Unlike DKA, the presence of insulin prevents progression of full-blown ketoacidosis. Also, insulin secretion is stimulated by ketones and fatty acids during prolonged fasting, thereby minimizing even further the formation of ketoacids. As in alcoholic ketoacidosis, intense ketonuria with a weak serum and urine reaction to nitroprusside is usually observed in starvation ketosis, suggesting predominance of β-hydroxybutyric acid. A slight increase in AG is usually seen. Since ketones compete with uric acid secretion in the proximal tubule, an elevation in uric acid level is not uncommon. Resumption of food intake and volume correction with 5% D5W and normal saline usually correct ketoacidosis.

Study Questions

Case 1 Two type 1 diabetic patients are admitted to the intensive care unit for management of severe diabetic ketoacidosis (DKA). One patient has acute kidney injury (AKI), glucosuria, and ketonuria. The other patient is on hemodialysis (HD) with no urine output. Their DKA was precipitated by pneumonia. Serum [HCO_3^-] is 8 mEq/L in both patients. You decide to treat both patients with normal saline and bicarbonate ($NaHCO_3$). Which one of the following patients requires more fluid and bicarbonate to improve volume status and acidosis?

A. Both require equal quantity of saline and bicarbonate
B. HD patient requires both more than the AKI patient
C. AKI patient requires both more than the HD patient
D. HD patient requires more bicarbonate than saline
E. AKI patient requires only saline

The answer is C. Volume status is different in both patients. The patient with AKI loses more water and electrolytes than HD patient with no urine formation. This is evident from glucosuria and ketonuria, which obligate water and salt loss. Therefore, volume depletion is rather severe in the patient with urine output due to osmotic diuresis, and requires more fluid than the HD patient. Because ketones are lost in the

urine and infusion of saline further lowers bicarbonate, recovery of serum [HCO_3^-] from these ketone bodies is slow once insulin is started. Therefore, the patient with AKI requires substantial repletion of volume and bicarbonate. Thus, answer C is correct.

Because of no urine output, the HD patient does not lose any ketones and, therefore, these ketones are retained in the body. Also, there is no osmotic diuresis and consequently no water loss. Following insulin administration, these ketones are converted into bicarbonate, and serum [HCO_3^-] improves much faster than that of the patient with AKI. Therefore, the patient requires less volume and little or no bicarbonate. Thus, other answers are incorrect.

Case 2 A type 2 diabetic man is on sodium-glucose cotransporter-2 (SGLT-2) inhibitor for 1 year. He presents to his primary care physician with complaints of nausea, vomiting, weakness, and abdominal pain for 4 days. He has some burning on urination. His blood pressure and pulse are normal. Serum glucose is 148 mg/dL, and he has acetone breath. Which one the following is the *most* likely diagnosis in this patient?

A. Alcohol ketoacidosis
B. Starvation ketoacidosis
C. Euglycemic diabetic ketoacidosis (DKA)
D. Lactic acidosis
E. Ingestion of isopropyl alcohol

The answer is C. Many case reports of euglycemic DKA have been reported since the introduction of SGLT-2 inhibitors in both type 1 and type 2 diabetic patients with normal or slightly elevated glucose levels. Relative lack of insulin and infection seems to precipitate DKA in these patients who are on SGLT-2 inhibitors. These patients have high glucagon levels, which may promote ketogenesis. Discontinuation of SGLT-2 inhibitor and institution of insulin improve ketoacidosis. Thus, answer C is correct.

Alcohol and starvation ketoacidosis are unlikely in view of slightly elevated glucose levels, as these two conditions are usually associated with low glucose levels. Lactic acid is also unlikely in view of normal blood pressure. Isopropyl alcohol is metabolized to acetone, but metabolic acidosis is unlikely in view of normal blood pressure. Thus, answers A, B, D, and E are incorrect.

Suggested Reading

Adrogué HJ, Madias NE. Diabetic and other forms of ketoacidosis. In: Jennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 313–50.

Dhatariya KK, Velllanki P. Treatment of diabetic ketoacidosis (DKA)/hyperglycemic hyperosmolar state (HHS): novel advances in the management of hyperglycemic crises (UK versus USA). Curr Diab Rep. 2017;17:33.
Fayfman M, Pasquel FJ, Umpierrez GE. Management of hyperglycemic crises. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Med Clin N Am. 2017;101:587–606.
Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. Clin Thrapeut. 2016;38:2654–64.
Inward CD, Chambers TL. Fluid management in diabetic ketoacidosis. Have we got it right yet? Arch Dis Child. 2002;86:443–5.
Joint British Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults. 2nd ed., 2013, pp 1–43. www.diabetes/org.UK.
Kamel KS, Halperin ML. Acid-base problems in diabetic ketoacidosis. N Engl J Med. 2015;372:346–54.
Kamel KS, Schreiber M, Carlotti APCP, et al. Approach to the treatment of diabetic ketoacidosis. Am J Kidney Dis. 2016;68:967–72.
Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32:1333–43.
McGuire LC, Cruickshank AM, Munro PT. Alcoholic ketoacidosis. Emer Med J. 2006;23:417–20.
Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. Metabolism. 2016;65:507–21.
Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: A historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care. 2014;37:3124–31.
Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: A predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care. 2015;38:1638–42.
Tran TTT, Pease A, Wood AJ, et al. Review of evidence for adult diabetic ketoacidosis management protocols. Front Endocrinol. 2017;8:1–13. (article 106).
Wrenn KD, Slovis CM, Minion G, et al. The syndrome of alcoholic ketoacidosis. Am J Med. 1991;91:11928.

Chapter 7
Toxin-Induced Acid-Base Disorders

In Chaps. 5 and 6, lactic acidosis and ketoacidosis were discussed. These acidoses are characterized by high anion gap (AG). Other causes of high AG metabolic acidosis include ingestion of alcohols, glycols, salicylates, acetaminophen (paracetamol), toluene, and paraldehyde. This chapter focuses on the following toxins that cause acid-base disorders:

1. Methanol
2. Ethylene glycol
3. Diethylene glycol
4. Propylene glycol
5. Isopropyl alcohol
6. Salicylates
7. Acetaminophen (5-Oxoproline or pyroglutamic acid)
8. Toluene
9. Paraldehyde

General Considerations

Ingestion of alcohols, such as ethanol, methanol, ethylene glycol, and diethylene glycol, or administration of propylene glycol generates not only hyperosmolality but also metabolic acidosis with high AG. Whenever ingestion of these toxins is suspected, it is important to measure and calculate serum osmolality to identify osmolal gap.

Osmolal gap is defined as the difference between the *measured* and *calculated* serum osmolality. Generally, the measured osmolality is 10 mOsm higher than the calculated osmolality. Values >10 mOsm represent the presence of an osmolal gap.

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_7

Note that in one study, the osmolal gap in healthy volunteers varied from −14 to 10 mOsm, suggesting that >10 is found to be abnormal. Elevated osmolal gap suggests the presence of osmotically active substances that are measured, but not included in the calculation of osmolality. Lactate, keto acids, and salicylate intoxication also cause high osmolal gap. Traditionally, the presence of an osmolal gap and an elevated anion gap is considered to represent the ingestion of toxic alcohols such as methanol, ethylene glycol, and others (Table 7.1).

In a suspected case of toxic alcohol ingestion, one can estimate its blood levels by using the following formula:

$$\text{Blood level}\left(\text{mg}/\text{dL}\right) = \frac{\text{Osmolal gap} \times \text{Molecular wt of alcohol}}{10}$$

However, the use of this formula may not be necessary, as the levels of many alcohols are available through the clinical laboratory.

The first step in the metabolism of all toxic alcohols is catalyzed by the enzyme alcohol dehydrogenase (ADH), which is the most critical step in metabolism. Administration of an antidote to inhibit the enzyme ADH prevents the toxic metabolites of the parent alcohol. Metabolism of ethanol was discussed in Chap. 6. Table 7.2 shows metabolic end products that cause toxicity.

Table 7.1 Contribution of some toxic substances to serum osmolality

Substance (100 mg/dL)	Molecular weight	mOsm/kg H_2O
Methanol	32	31
Ethylene glycol	62	16
Diethylene glycol	106	9.4
Propylene glycol	76	13
Isopropanol	60	17
Salicylate	180	6
Acetone	58	17
Paraldehyde	132	8

Table 7.2 Toxic metabolites of alcohols and acetylsalicylate (aspirin)

Substance	Toxic metabolite (s)	Comment
Methanol	Formic acid	Blindness and mortality high, if not recognized and treated early
Ethylene glycol	Glycolic acid, oxalic acid	Acute kidney injury, ↓ cardiac contractility, mortality high, if not treated early
Diethylene glycol	2-hydroxyethoxyacetic acid	Acute kidney injury, neurotoxicity, GI toxicity, high mortality, if not recognized
Propylene glycol	Lactic acid	Hospital-acquired lactic acidosis, minimal clinical manifestations
Isopropyl alcohol	Acetone	No acidosis, acetone breath, low mortality
Acetylsalicylic acid (aspirin)	Salicylic acid	Respiratory alkalosis and metabolic acidosis in adults, metabolic acidosis in children

Management of toxic alcohol ingestion includes (1) gastric lavage, (2) ethanol, (3) antidote to inhibit the enzyme ADH, and (4) renal replacement therapies. Details of these therapeutic modalities will be presented later in the chapter.

Let us discuss each one of these toxins and others in detail.

Methyl Alcohol (Methanol)

- Common names: methyl alcohol, wood alcohol, wood spirit, and carbinol
- Sources: antifreeze, additive to gasoline and diesel oil, windshield wiper fluid (most common abuse in the USA), dyes, varnishes, and cheap alcohols
- Lethal dose is 30 mL of absolute methanol
- Easily absorbed from the gastrointestinal (GI) tract. Other less routes of exposure are inhalation and skin absorption
- Half-life of methanol in low dose is 14–24 h, and in higher doses the half-life is prolonged to 24–30 h

Metabolism

As shown in Fig. 7.1, methanol is metabolized to formaldehyde by the enzyme ADH, which is then converted to formic acid (formate) by aldehyde dehydrogenase (ALDH). Both enzymes require the reduction of NAD^+ to NADH $+H^+$; thus the ratio of NADH $+H^+/NAD^+$ is increased. The increase in this ratio converts pyruvate to lactate. When folinic acid (folate) is given, formic acid is rapidly converted to CO_2 and water. Methanol is not itself toxic, but its metabolites, formaldehyde and formic acid, are extremely toxic.

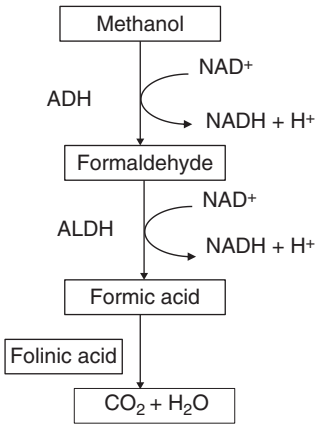

Fig. 7.1 Metabolism of methanol. ADH alcohol dehydrogenase, ALDH aldehyde dehydrogenase

Clinical Manifestations

Mostly due to formic acid (formate)

- Signs and symptoms of methanol intoxication are related to central nervous and GI systems:
  - Lethargy, headache, confusion, and vertigo are common.
  - Eye pain, blurred vision, photophobia, and blindness are common at presentation in 50% of patients.
  - Hyperemia of optic disc, fixed and dilated pupils, and papilledema are the ophthalmoscopic findings, which are related to formaldehyde.
  - Nausea, vomiting, pancreatitis, and abdominal pain are common GI complaints.
- Coingestion of ethanol delays the manifestations of methanol intoxication.

Diagnosis

The following labs and clinical suspicion are important in making the diagnosis of methanol intoxication.

- Serum electrolytes, BUN, creatinine, glucose, serum osmolality, serum Ca^{2+}, Mg^{2+}, ethanol, ethylene glycol, and ketone levels, urine microscopy, and ABG
- Visual impairment, high osmolal gap, and high AG metabolic acidosis should alert the physician of methanol intoxication and warrant immediate treatment to prevent blindness. High AG is contributed by formic acid, lactic acid, and keto acids.

Treatment

The criteria for the initiation of therapy in patients with known or suspected methanol poisoning are:

Plasma methanol level of ≥ 20 mg/dL

or

Documented recent history of toxic amounts of methanol ingestion and an osmolal gap >10 mOsm/L

or

Suspected methanol ingestion and at least two of the following criteria:

Arterial pH < 7.30
Serum [HCO_3^-] < 20 mEq/L
Serum osmolal gap > 10 mOsm/kg H_2O

Immediate supportive care includes:

1. Hydration with normal saline and glucose for hypoglycemia
2. Intravenous $NaHCO_3$ to maintain blood pH > 7.2
3. Intravenous folinic acid (1 mg/kg) one dose and then folate supplementation to accelerate formate metabolism to CO_2 and water by tetrahydrofolate synthetase. This may benefit some alcoholics with folate deficiency
4. The American Academy of Clinical Toxicology recommendations are:
   - *Fomepizole* (4-methylpyrazole), the drug of choice in the USA.
   - *Ethanol*, if fomepizole not available.
   - Fomepizole is a competitive inhibitor of ADH, and the recommended dosages are as follows:

     Without dialysis

     Loading dose: 15 mg/kg
     Maintenance dose: 10 mg/kg Q12 h for four doses
     After 48 h or four doses, 15 mg/kg Q12 h until methanol levels are <20 mg/dL

     With dialysis

     Same doses as above except that the drug is given 6 h after the first dose and then Q4 h thereafter

Ethanol is a substrate for ADH, and its administration decreases the metabolism of methanol. It has 10–20 times greater affinity for ADH than other alcohols. Ethanol at a serum concentration of 100 mg/dL inhibits completely the enzyme ADH. The recommended dosage is as follows:

Dose	Absolute alcohol	10% i.v. solution
Loading	600 mg/kg	7.6 mL/kg
Maintenance (nondrinker)	66 mg/kg/h	0.83 mL/kg/h
Maintenance (drinker)	154 mg/kg/h	1.96 mL/kg/h
Maintenance during dialysis (nondrinker)	169 mg/kg/h	2.13 mL/kg/h
Maintenance during dialysis (drinkers)	257 mg/kg/h	3.26 mL/kg/h

Hemodialysis

With the introduction of fomepizole, routine use of hemodialysis has diminished, and it has become an adjunctive therapy. However, hemodialysis is indicated in the following situations:

1. Ethanol-treated patient with methanol level >50 mg/dL
2. Renal dysfunction
3. Visual impairment

4. Severe acidemia

- It is important to understand the advantages and disadvantages of each of these treatment modalities for judicious use in the management of methanol poisoning (Table 7.3).
- Severe acidemia has a prognostic significance. Serum [HCO_3^-] <20 mEq/L carries 10% mortality, whereas [HCO_3^-] <10 mEq/L has the mortality of 50%. Therefore, maintenance of arterial pH >7.2 is important.
- It should be noted that intermittent hemodialysis is the modality of choice for methanol poisoning and continuous renal replacement therapies are acceptable alternatives if the patient cannot tolerate hemodialysis or it is not available

    1. Methanol clearance is more (an average of 208 mL/min) with hemodialysis comrade to an average of 36.7 mL/min with continuous renal replacement therapy (Roberts DM, Yates C, Megarbane B, et al. *Crit Care Med* 2015; 43:461–47).

Table 7.3 Advantages and disadvantages of antidotes and dialysis

Treatment modality	Advantages	Disadvantages
Fomepizole	High affinity for alcohol dehydrogenase (ADH). Plasma concentration of 0.8 μg/mL inhibits ADH activity	Not immediately available in all clinical facilities
	Effective at low serum concentrations	Expensive ($ 4000–5000)
	Few adverse effects other than slight increases in AST/ALT	Approved only for methanol and ethylene glycol poisoning
	Admission to intensive care units is not always necessary	No oral form available
	No effect on serum osmolal gap	
Ethanol	Easily available	Lower affinity for ADH than fomepizole
	Inexpensive	ICU monitoring required
	Can be given i.v. or orally	Maintenance of 100 mg/dL necessary to inhibit ADH
		Ethanol intoxication in some patients
		↑ Serum osmolal gap
Dialysis	Highly efficient to remove both primary alcohol and its metabolites	Invasive
	Improves renal function	Expensive
	Improves acidemia with HCO_3^- dialysis bath	Unavailability in many countries
	Decreases hospital stay	
	Rapid improvement in signs and symptoms of methanol poisoning	

Ethylene Glycol (EG)

- Colorless, odorless, and sweet-tasting alcohol.
- Sources: antifreeze, deicers, and many industrial products.
- EG intoxication is more common than methanol intoxication.
- Oral ingestion of EG is the most common route of EG intoxication.
- EG is metabolized to glycolic and oxalic acids (Fig. 7.2).
- Glycolic acid is the major cause of high AG acidosis.
- Oxalic acid is the major cause of AKI, myocardial, neurologic, and pulmonary dysfunction due to deposition of calcium oxalate in these organ systems.
- Lethal dose of EG is 1.4 mL/kg.

Metabolism

EG is converted into glycolaldehyde by the enzyme ADH, which is further metabolized to glycolic acid by aldehyde dehydrogenase. During these two reactions, NAD is reduced to NADH. Glycolic acid is the major acid of EG metabolism (Fig. 7.2). About 1–2% of glycolic acid is metabolized to oxalic acid, which is precipitated in the urine as calcium oxalate crystals (Fig. 7.3). Glycolic acid is the major acid in the metabolism of EG. About 98% of glycolic acid is transaminated to glycine by the enzyme alanine glyoxalate aminotransferase.

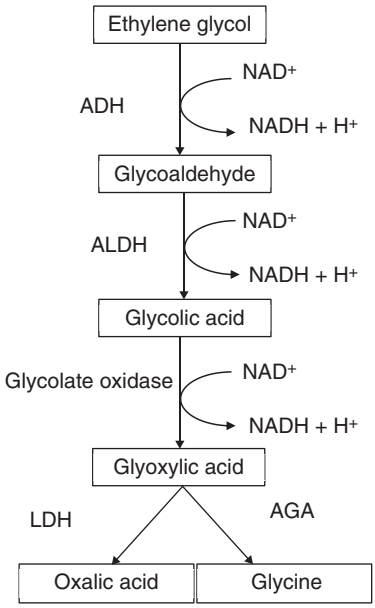

Fig. 7.2 Metabolism of ethylene glycol. ADH alcohol dehydrogenase, ALDH aldehyde dehydrogenase, LDH lactate dehydrogenase, AGA alanine glyoxalate aminotransferase

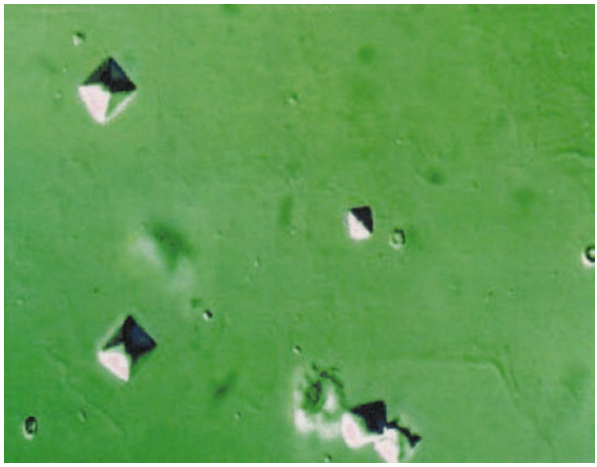

Fig. 7.3 Calcium oxalate dihydrate crystals (envelope-like appearance). Calcium monohydrate crystals may also be seen, which have a dumbbell appearance

Clinical Manifestations (Classified into Three Stages)

Stage 1 (0.5–12 h after ingestion): transient inebriation and euphoria with progression to cerebral edema and coma.
Stage 2 (12–24 h after ingestion): tachycardia and hypertension, severe metabolic acidosis. ARDS may develop. Most deaths occur during this stage.
Stage 3 (24–72 h after ingestion): oliguria, anuria, and severe renal dysfunction, requiring hemodialysis.

Note that neurologic, cardiopulmonary, and renal abnormalities can present at the time of admission in some patients.

Coingestion of ethanol delays the manifestations of ethylene glycol intoxication.

Diagnosis

- Serum electrolytes, BUN, creatinine, glucose, serum osmolality, serum Ca^{2+}, Mg^{2+}, ethanol, EG, ketones, lactate, urine microscopy, and ABG.
- Severe high AG metabolic acidosis, increased osmolal gap, and at times the presence of oxalate crystals in the urine (Fig. 7.3) are suggestive of EG intoxication.
- Oxalate crystals may appear like dumbbells or like needles as well.
- Note that osmolal gap is not always present because of small contribution of osmoles by EG compared to other alcohols and also the absence of glycolic acid due to rapid conversion to oxalic acid.
- Hypocalcemia may be present.
- High AG and high osmolal gap are associated with high mortality.

- Several compounds can interfere with the assay of EG and give false-positive levels. For example, 2,3-butanediol ingestion can be mistakenly identified as EG when measured by gas chromatography. False-positive levels of EG can be documented in patients with lactic acidosis and ketoacidosis when measured with spectrophotometry. Propylene glycol and glycerol interfere with EG and lower its levels.
- In addition to the above interfering compounds, an inherited metabolic disorder can present as EG intoxication. This disorder is due to deficiency of complex I in the mitochondrial oxidative phosphorylation. Although EG levels are absent, both disorders can present with neurologic, cardiac, and renal problems. Elevated lactate and metabolic acidosis are present in both conditions. However, crystalluria and glycolic acid are absent in mitochondrial disease.

Treatment

The criteria for the initiation of therapy in patients with known or suspected EG poisoning are:

Plasma EG level of ≥ 20 mg/dL
or
Documented recent history of toxic amounts of EG ingestion and an osmolal gap >10 mOsm/L
or
Suspected EG ingestion and at least two of the following criteria:

Arterial pH <7.30
Serum [HCO_3^-] <20 mEq/L
Serum osmolal gap >10 mOsm/L
Presence of oxalate crystals in urine

The treatment guidelines for EG ingestion are shown in Table 7.4 [1].

Diethylene Glycol

- Diethylene glycol (DEG) is a clear, colorless, and odorless liquid with sweetish taste.
- Present in antifreeze formulations, break fluids, lubricants, wallpaper strippers, heating fuel, inks, paper, and packaging materials.
- Cases of fatalities came from ingestion of sulfanilamide elixirs used in many countries, including the USA.
- Readily absorbed following oral ingestion and skin application.
- Toxic dose is 0.14 mg/kg, and lethal dose is 1–1.63 g/kg.
- DEA is excreted 80% unchanged in the kidney, but 20% is 2-hydroxyethoxyacetic acid.

Metabolism

DEG consists of two EG molecules linked by a stable ether bond. However, DEG is not metabolized to two EG molecules. Indeed, it is oxidized to 2-hydroxyethoxyacetaldehyde by ADH (Fig. 7.4), which is then rapidly metabolized to 2-hydroxyethoxyacetic acid by aldehyde dehydrogenase. Both enzymes require the conversion of NAD^+ to $NADH+H^+$. Studies have shown that 2-hydroxyethoxyacetic acid does not undergo any further oxidation. It is the 2-hydroxyethoxyacetic acid that is toxic to the kidney, causing AKI. Also, this compound causes high AG metabolic acidosis.

Table 7.4 Treatment guidelines for EG ingestion

Treatment	Indications
Supportive care	Volume depletion and hypoglycemia: correct volume deficit with normal saline and D5W to improve glucose levels
	$NaHCO_3$, if pH <7.20
	Pyridoxine and thiamine, particularly in alcoholics, to expedite glyoxylate metabolism
	Follow serum EG levels, Ca^{2+}, creatinine, lactate, and ABG
	Ingestion of multiple substances with depressed level of consciousness
Fomepizole	Altered mental status
	Inadequate ICU staffing or laboratory support to monitor ethanol administration
	Relative contraindication to ethanol (liver disease)
	Critically ill patient with high AG metabolic acidosis of unknown etiology and potential exposure to EG
Ethanol	Unavailability of fomepizole
Hemodialysis	Severe metabolic acidosis refractory to fomepizole and ethanol or $NaHCO_3$
	Anuria
	Renal failure

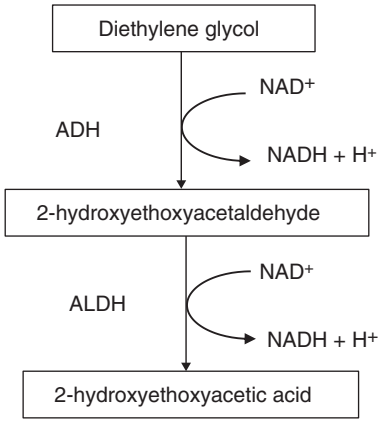

Fig. 7.4 Metabolism of diethylene glycol. ADH alcohol dehydrogenase, ALDH aldehyde dehydrogenase

Clinical Manifestations

DEG manifestations can be divided into three phases:

Phase 1. GI symptoms (nausea, vomiting, abdominal pain, diarrhea) and inebriation as well as development of metabolic acidosis.
Phase 2. Worsening of metabolic acidosis, acute kidney injury, and hepatic injury. Oliguria, hyperkalemia, transaminitis, and volume depletion with hypotension can be seen frequently.
Phase 3. Severe peripheral or cranial nerve palsies, particularly seventh nerve palsy. CNS manifestations include depression, confusion, and coma. Cardiac arrhythmias are not uncommon.

The above signs and symptoms may overlap, and at times a clear-cut distinction of the above phases cannot be made. This is related to duration of ingestion of DEG and coingestion of alcohol may obscure these phases.

Diagnosis

- Serum electrolytes, BUN, creatinine, glucose, serum osmolality, serum Ca^{2+}, Mg^{2+}, methanol, EG, ketones, lactate, urine microscopy, and ABG.
- Severe high AG metabolic acidosis, increased osmolal gap, and peripheral or cranial nerve palsies are suggestive of DEG intoxication.
- Note that osmolal gap is not always present because of small contribution of osmoles by DEG compared to other alcohols.

Treatment

Treatment is similar to other alcohol intoxication. Inhibition of ADH by either ethanol or fomepizole is initial therapy for DEG intoxication. Hemodialysis is also helpful, but its use has been limited.

Propylene Glycol (PG)

- PG is used as a diluent in i.v. and oral drugs, including phenytoin, diazepam, lorazepam, phenobarbital, nitroglycerin, hydralazine, and trimethoprim-sulfamethoxazole.
- Most of the cases of PG intoxications are from i.v. administration of drugs.
- Toxicity of PG occurs at blood concentrations >100 mg/dL.
- Patients with liver and kidney dysfunction are at risk for PG toxicity.

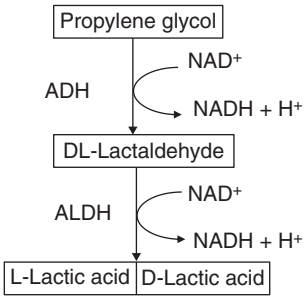

Fig. 7.5 Metabolism of propylene glycol to L- and D-lactic acid. ADH alcohol dehydrogenase, ALDH aldehyde dehydrogenase

Metabolism

PG is metabolized to DL-lactaldehyde by the enzyme ADH, further conversion to L- and D-lactic acid by ALDH. Both reactions reduce NAD^+ to NADH $+H^+$. Lactaldehyde is also converted to methylglyoxal and then to D-lactic acid (not shown in Fig. 7.5).

Clinical Manifestations

Include disorientation, depression, nystagmus, ataxia, hypotension, and cardiac arrhythmias.

Diagnosis

- Metabolic acidosis with high AG due to lactic acid (both L- and D-forms). Renal failure occurs in some patients.

Treatment

Includes discontinuation of the offending agent. Hemodialysis helps in correcting renal failure and lowering PG levels.

Isopropyl Alcohol

- Usually called rubbing alcohol
- Sources: rubbing alcohol, cleaning agents, deicer, and industrial solvents
- Route of exposure: skin and GI tract absorption as well as inhalation by lungs
- Metabolized to acetone by ADH

Clinical Manifestations

Depend on serum levels of isopropanol: levels >150 mg/dL are associated with hypotension and coma; levels >400 mg/dL carry poor prognosis.

Diagnosis

- High serum osmolality with large osmolal gap and normal acid-base disorder are common findings in subjects with isopropyl alcohol intoxication.
- Acetone breath and positive serum and urine nitroprusside reaction usually mislead to the diagnosis of diabetic ketoacidosis. Only serum glucose levels differentiate between these two conditions.
- If high AG metabolic acidosis is present, suspect lactic acidosis due to hypotension.

Treatment

Supportive care, as the intoxication is self-limited. Hemodialysis is indicated in subjects with serum levels >200 mg/dL and hypotension.

Salicylate Intoxication

- Aspirin (acetylsalicylic acid or ASA) is the most commonly used salicylate.
- Exposure is topical and oral forms. ASA is readily absorbed in the GI tract, and salicylate is responsible for systemic toxic effects.
- Intake of ASA is usually accidental in children and suicidal or intentional in adults.
- Serum half-life of salicylate is 2–4 h at low doses and approximately 12 h with therapeutic doses and can be prolonged to 15–30 h or more with toxic doses.
- 2–30% of salicylate is excreted unchanged in the urine, with less renal excretion occurring in acidic urine or in patients with renal failure.
- Metabolic effects are:

  1. Uncoupling of oxidative phosphorylation and decreased ATP production
  2. Inhibition of conversion of α-ketoglutarate to succinate and succinate to fumarate, resulting in lipolysis, ketone formation, and stimulation of glycolysis
  3. Acid-base disorder in adults: Initially respiratory alkalosis due to stimulation of medullary respiratory center by salicylate and hyperventilation. Subsequently, metabolic acidosis develops due to lactic acid and ketoacid production. Respiratory alkalosis seems to be the main reason for lactic acid production

4. In children, metabolic acidosis predominates initially
5. Urate excretion is low with low doses of salicylate and high with high doses of salicylate

Clinical Manifestations

Depend on acute or chronic ingestion of ASA.

Acute manifestations: Nausea, vomiting, abdominal pain, hematemesis, tachypnea, tinnitus, deafness, lethargy, confusion, coma, and seizures.

Chronic manifestations: Occur mostly in elderly patients with chronic use of ASA. Most of the manifestations are similar to those of acute intoxication except for GI symptoms. Patients appear ill, and neurologic symptoms are more prominent, including agitation, confusion, slurred speech, coma, and seizures.

Diagnosis

- History is extremely important, if it can be obtained. Type of salicylate, amount ingested, time of ingestion, long-term use, use of other medications, and history of renal, hepatic, cardiac, and psychiatric diseases should help therapeutic decision.
- Fever is common in children.
- Serum electrolytes, BUN, creatinine, and glucose, Ca^{2+}, lactate, and ketones should be obtained.
- ABG: Respiratory alkalosis with AG metabolic acidosis with hyperventilation and tinnitus should suggest the diagnosis of salicylate poisoning.
- Urine pH is important, as acid pH increases salicylate toxicity.
- Serial serum salicylate levels are extremely important for therapeutic consideration.
- Obtain chest x-ray for edema and EKG for arrhythmias.

Treatment

Four goals for symptomatic acute or chronic toxicity, as there are no antidotes:

1. Supportive care
2. Reduce GI absorption of salicylate
3. Promote renal excretion of salicylate

4. Lower plasma levels of salicylate by hemodialysis

   - *Supportive care*: Should start in the Emergency Department for the following:
     - Endotracheal intubation for protection of airways, hypoxia, and continuation of hyperventilation to prevent further drop in pH
     - Correction of volume deficit and electrolyte abnormalities to maintain hemodynamic stability
   - *Reduce GI absorption of salicylate*: Use oral activated charcoal at 1 g/kg to a maximum of 50 g in children and 100 g in adults. The minimum dose is 30 g. Repeat the dose of charcoal. Use of sorbitol with charcoal is advocated in adults by some physicians. The use of ipecac is controversial.
   - *Promote renal excretion of salicylate*: Adequate fluid administration and alkalinization of urine promote the excretion of salicylic acid. Acidosis promotes tissue transfer of salicylate, particularly into the brain, and alkalinization prevents tissue penetration. One way to alkalinize the body fluids and urine is to give 1.5 L of 150 mEq/L of $NaHCO_3$ solution over 4 h. Blood pH should be followed with serum K^+ and Ca^{2+}. Continue urinary alkalinization until serum salicylate levels drop to therapeutic range (30 mg/dL).
   - *Lowering plasma levels of salicylate by hemodialysis*: Hemodialysis is indicated for serum salicylate levels > 120 mg/dL, refractory acidosis, fluid overload, renal failure, noncardiogenic pulmonary edema, coma, and seizures. Hemoperfusion is efficient in removing salicylate, but may not be that effective in correcting renal failure or fluid overload or severe acidosis. Peritoneal dialysis is not effective. Hemodialysis is also effective in symptomatic patient with chronic overdose, and salicylate levels exceed 60–80 mg/dL.

5-Oxoproline (Pyroglutamic Acid)

- Pyroglutamic acid is a degradative product of reduced glutathione (GSH), and its accumulation in blood causes high AG metabolic acidosis (Fig. 7.6).
- The synthesis and degradation of glutathione occur by reactions of the γ-glutamyl cycle.
- Glutathione is a tripeptide, consisting of glutamate, cysteine, and glycine (usually written as l-γ-glutamyl-L-cysteinylglycine). The synthesis and degradation of glutathione involve six enzymes, two enzymes for synthesis (γ-glutamylcysteine synthetase and glutathione synthetase) and four enzymes for degradation (γ-glutamyl transpeptidase, γ-glutamylcyclotransferase, 5-oxoprolinase, and dipeptidase), as shown in Fig. 7.6.
- GSH is found in most cells in high (millimolar) concentrations. It has several functions, including amino acid transport and maintenance of thiol/disulfide balance.

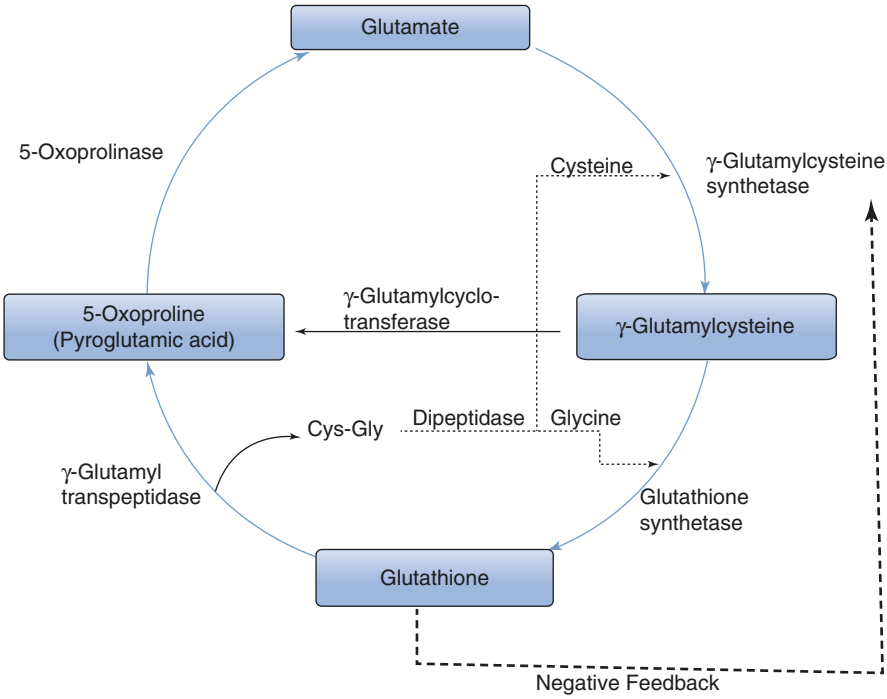

Fig. 7.6 Simplified γ-glutamyl cycle

- Under normal circumstances, glutathione inhibits γ-glutamylcysteine synthetase so that excess production of γ-glutamylcysteine is prevented. When glutathione levels decrease, the feedback inhibition is relieved, resulting in accumulation of γ-glutamylcysteine and conversion to pyroglutamic acid by the enzyme γ-glutamylcyclotransferase (Fig. 7.6).
- Elevated levels of pyroglutamic acid in blood cause high AG metabolic acidosis. Initially, pyroglutamic acidemia was described in infants with inherited deficiencies of glutathione synthetase and 5-oxoprolinase.
- These inherited enzyme deficiencies are rather rare, but acquired pyroglutamic acidemia and aciduria have been reported in adults in several clinical settings.
- Clinical conditions associated with pyroglutamic acidosis are sepsis, malnutrition, pregnancy, vegetarian, and modified diets.
- Drugs that cause pyroglutamic acidosis include acetaminophen (paracetamol), vigabatrin, an antiepileptic drug, monosodium glutamate, and antibiotics such as flucloxacillin or netilmicin.
- The common underlying mechanism for pyroglutamic acidemia and aciduria is depletion of tissue glutathione. However, vigabatrin and flucloxacillin seem to inhibit the enzyme 5-oxoprolinase.

Diagnosis

- History of drugs and antibiotics is very important. Chronic clinical conditions, such as rheumatoid arthritis, disc diseases, trauma, neuropathies, and surgeries, can give a clue of pain medication and antibiotic use.
- Unexplained AG metabolic acidosis, like D-lactic acidosis, may be a clue to the diagnosis of pyroglutamic acidosis. Osmolal gap is normal.

Treatment

Includes discontinuation of the offending agent. Hemodialysis is needed to improve refractory acidosis and renal failure. N-acetylcysteine (NAC) can provide cysteine to replenish glutathione levels. It is, therefore, suggested that NAC may improve pyroglutamic acidemia.

Toluene

- Other names: methylbenzene or phenylmethane.
- Sources: acrylic paints, varnishes, paint thinners, glues, adhesives, shoe polish, gasoline, transmission fluid, and industrial solvents.
- Poisoning occurs by inhalation to induce euphoria.
- Children and adolescents are common users with male predominance.
- Levels of 200 PPM (parts per million) are dangerous.
- Metabolized to benzyl alcohol, then to benzoic acid, and finally to hippuric acid (hippurate).
- Hippurate is rapidly excreted by the kidneys, if renal function is normal.
- Because of this rapid excretion, hippurate levels are normal at the time of evaluation.

Clinical Manifestations

- Primarily CNS effects, such as euphoria, confusion, dizziness, stupor, and coma. Bronchospasm is common.
- Chronic abuse leads to neuropsychosis, ataxia, optic and peripheral neuropathies, blindness, and decreased cognitive ability.

Diagnosis

- High AG metabolic acidosis is common when serum hippurate levels are high; otherwise, hyperchloremic metabolic acidosis with severe hypokalemia is the common presentation, and serum hippurate levels are normal.
- Hyperchloremic metabolic acidosis and hypokalemia are thought to be due to distal renal tubular acidosis. Some patients also develop Fanconi syndrome.
- Acute kidney injury is also common, which is due to hypotension and/or rhabdomyolysis.

Treatment

Includes supportive care and volume expansion with KCl supplementation. There is no antidote. Hemodialysis is recommended for severe renal failure.

Paraldehyde

- Used as a sedative and also for treatment of delirium tremens.
- It is replaced by many other drugs for delirium tremens, so cases of paraldehyde intoxication are rare.
- Metabolized to probably acetaldehyde and acetic acid, causing a high AG metabolic acidosis.
- No osmolal gap is seen.

Treatment

Removal of the drug and supportive care

Study Questions

Case 1 A 54-year-old woman was admitted through the Emergency Department (ED) for shortness of breath, "unwell" feeling, and weakness of few days duration. Her blood pressure was 114/51 mmHg with a pulse rate of 69 beats per minute. She was afebrile. Her medical history is significant for cervical and lumbosacral disc disease, hypertension, depression, anxiety, ataxia, and chronic pulmonary obstructive disease. She had carpal tunnel and cervical disc surgery, cholecystectomy, and hysterectomy. Her medications included Combivent (ipratropium bromide 18 μg and albuterol 90 μg) one puff every 8 h; Metoprolol 12.5 mg twice daily; Klonopin

(clonazepam) 0.5 mg every 8 h, as needed; and Vicodin ES (hydrocodone bitartrate 7.5 mg and acetaminophen 750 mg) every 8 h, as needed. The patient was previously admitted with similar complaints and found to have a high AG metabolic acidosis and acute kidney injury, requiring short-term hemodialysis.

Laboratory results are shown in the following table. Hemoglobin was 13.4 g% and a platelet count of 430,000. Serum glucose was 80 mg/dL. ABG: pH of 7.20, pCO_2 15 mmHg, pO_2 91 mmHg, and calculated HCO_3^- of 6 mEq/L. The AG was 16. Other pertinent laboratory results are normal. Serum osmolality was 293 mOsm/kg H_2O. Serum ketones and lactate were negative, and urinalysis was normal.

Hospital day	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	Creatinine (mg/dL)	BUN (mg/dL)	AG (mEq/L)	Albumin (g/dL)	pH
Admission	138	4.6	114	8	0.87	10	16	4.4	7.20
Day 2	143	4.8	119	11	0.59	11	13	3.9	7.31
Day 3	141	3.6	109	18	0.55	9	14	3.4	
Day 4	142	3.2	107	25	0.48	8	10	3.3	
Day 5	140	4.1	100	33	0.55	8	7	3.6	

Question 1 Characterize the acid-base disorder in ED.

Answer Based on pH and pCO_2 and serum [HCO_3^-], the acid-base disorder is high AG metabolic acidosis and respiratory alkalosis.

Question 2 Is calculation of osmolal gap important?

Answer Yes. In this patient, the osmolal gap is 6 mOsm/L. Therefore, methanol, ethylene glycol, ketoacidosis, and lactic acidosis (lactate levels are normal) can be excluded.

Question 3 Is aspirin overdose possible in this patient?

Answer Yes. However, the initial acid-base disorder in aspirin overdose is respiratory alkalosis followed by the development of high AG metabolic acidosis. In this patient, serum salicylate levels were normal, excluding the diagnosis of aspirin overdose.

Question 4 How does this acid-base disorder differ from that of toluene inhalation?

Answer Toluene inhalation causes a transient high AG metabolic acidosis and then hyperchloremic (non-AG) metabolic acidosis. In this patient, a slight increase in AG existed until the third day of admission, excluding the possibility of toluene inhalation. Also, the patient did not have any clinical manifestations of toluene inhalation or ingestion.

Question 5 What other laboratory tests you order at this time based on her medications?

Answer She is on high doses of acetaminophen (750 mg Q8 h); ordering urinary pyroglutamic acid is appropriate.

Question 6 What is the diagnosis of her high AG metabolic acidosis with normal osmolal gap?

Answer Her urinary pyroglutamic acid level was >11500 mmol/mol creatinine (reference range 0–100 mmol/mol creatinine). Also, acetaminophen and its metabolites were present. Therefore, the diagnosis was pyroglutamic acidosis due to daily high doses of acetaminophen (Tylenol) use. Tylenol depletes GSH, which promotes pyroglutamic acid production. She was started on fentanyl patch, and her serum [HCO_3^-] for the last 2 years has been normal.

Case 2 A 17-year-old female student is admitted for confusion and acute kidney injury. She is able to give some history that she had a fight with her boyfriend 2 days ago and she drank some liquid that was in their garage. She has no other significant medical or illicit drug history. In the ED, her vital signs are stable. Other than altered mental status and confusion, her physical examination is normal. She weighs 60 kg. Laboratory results are as follows:

Serum	Urine
Na^+ = 141 mEq/L	Osmolality = 320 mOsm/kg H_2O
K^+ = 4.2 mEq/L	pH = 5.2
Cl^- = 110 mEq/L	Protein = trace
HCO_3^- = 7 mEq/L	Blood = negative
BUN = 28 mg/dL	Urine sediment = envelope-like crystals
Creatinine = 1.8 mg/dL	
Glucose = 72 mg/dL	
Serum osmolality = 312 mOsm/kg H_2O	
ABG = pH 7.21, pCO_2 17 mmHg, pO_2 94 mmHg, calculated HCO_3^- 6 mEq/L	

Question 1 Characterize the acid-base disorder.

Answer High AG metabolic acidosis with respiratory alkalosis.

Question 2 What is her osmolal gap?

Answer Osmolal gap is the difference between measured serum osmolality and calculated serum osmolality. Therefore, her osmolal gap is 16 (312–296 = 16 mOsm), which is high.

Question 3 What is your diagnosis of this acid-base disorder?

Answer The presence of calcium oxalate crystals (envelope-like) in the urine sediment is the clue for her acid-base disturbance, which is ethylene glycol ingestion. One of the final products of ethylene glycol is oxalic acid, which is excreted as oxalate.

Question 4 What is your initial management?

Answer Antidote for ethylene glycol is fomepizole. The initial dose is 15 mg/kg followed by 10 mg/kg every 12 h for four doses. Continue fomepizole, if ethylene glycol levels are not below 20 mg/dL. At the same time, hydration with D5W and 3 ampules (150 mEq) of $NaHCO_3$ to run at 120 mL/h to improve volume status should be started.

Question 5 Is dialysis needed in this patient?

Answer Yes, if no improvement in renal function and metabolic acidosis following adequate hydration and administration of fomepizole and $NaHCO_3$ (see Table 7.4 for indications of dialysis).

Case 3 A 55-year-old man with chronic alcoholism presents to the ED with agitation, blurred vision, and eye pain. Blood pressure and pulse rate are normal. He is afebrile. He has a high AG metabolic acidosis with an osmolal gap of 26 mOsm/L.

Which one of the following toxic alcohol ingestions is the MOST likely cause of his symptoms?

A. Ethanol
B. Ethylene glycol
C. Methanol
D. Toluene
E. Isopropyl alcohol

The answer is C. Only formic acid formed from methanol is toxic to the optic nerve, causing visual impairment, blurred vision, eye pain, and blindness. Therefore, early institution of fomepizole is recommended to inhibit ADH and conversion of methanol to formaldehyde and formic acid.

Case 4 A 45-year-old man was brought by his wife to the Emergency Department for confusion and acetone breath. As per his wife, he drinks alcohol every day. Pertinent labs reveal a high serum osmolality with large osmolal gap and normal acid-base values. Based on the above information, which one of the following alcohols he consumed?

A. Ethanol
B. Methanol
C. Ethylene glycol

D. Isopropyl alcohol
E. Diethylene glycol

The answer is D. Isopropyl alcohol is usually called rubbing alcohol, and alcoholics occasionally drink it when ethanol is not available. It is metabolized to acetone, and urine is positive for ketones. One needs to rule out diabetic ketoacidosis because of acetone breath by determining serum glucose levels, which are normal in individuals with isopropyl alcohol ingestion. There are no acid-base disorders other than high serum osmolality and large osmolal gap because of isopropyl alcohol. Thus, answer D is correct. Treatment is supportive, as the intoxication is self-limited. However, hemodialysis is indicated in individuals with serum levels of isopropyl alcohol > 200 mg/dL and hypotension.

Other answers are incorrect because they cause acid-base disorders as well as electrolyte abnormalities.

Case 5 A 50-year-old man was admitted with severe abdominal pain and vomiting. CT of abdomen was normal. The patient has no complaints of eye problems. Labs indicate increase in serum creatinine and increased osmnolality and osmolal gap. Arterial blood gases show a high AG metabolic acidosis. He became oliguric and hyperkalemic, requiring hemodialysis. Two days later, he developed bilateral facial palsy. Urinalysis is normal. Which of the following alcohols is most likely cause of his clinical status?

A. Ethanol
B. Ethylene glycol
C. Methanol
D. Diethylene glycol
E. Isopropyl alcohol

The answer is D. The clinical manifestations, particularly, bilateral facial palsy (seventh nerve palsy), are rather common in patients with diethylene glycol intoxication. Thus, answer D is correct.

Ethanol and methanol rarely cause neurologic complications. Although ethylene glycol may present with neurologic complications, the urinalysis is normal (without oxalate crystals). Therefore ethylene glycol poisoning is unlikely. Thus, answers A, B, C, and E are incorrect.

Case 6 Fomepizole is an inhibitor of alcohol dehydrogenase (ADH). Which one of the following agents does not require ADH?

A. Ethanol
B. Methanol
C. Ethylene glycol
D. 5-Oxoproline
E. Diethylene glycol

The answer is D. All of the alcohols, including isopropyl alcohol, require ADH for their metabolism except 5-oxoproline. Therefore, answer D is correct.

Case 7 Which one of the following agents initially causes respiratory alkalosis and then high AG metabolic acidosis in an adult subject?

A. Toluene
B. Tenofovir
C. Acetylsalicylic acid (ASA)
D. Flucloxacillin
E. None of the above

The answer is C. ASA causes initially respiratory alkalosis due to stimulation of medullary respiratory center and hyperventilation. Subsequently, metabolic acidosis develops due to lactic acid and keto acid production. Respiratory alkalosis seems to be the main reason for lactic acid production. Thus, answer C is correct. In children, metabolic acidosis is the initial presentation of ASA ingestion.

Toluene causes hippuric acid and tenofovir causes lactic acid, whereas flucloxacillin causes pyroglutamic acid.

References

1. Barceloux DG, Krenzelok EP, Olson K, et al. American academy of clinical toxicology practice guidelines on the treatment of ethylene glycol poisoning. J Toxicol Clin Toxicol. 1999;37:537–60.

Suggested Reading

Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med. 2009;360:2216–23.
Cerdá J, Tolwani AJ, Warnock DG. Critical care nephrology: management of acid-base disorders with CRRT. Kidney Int. 2012;82:9–18.
Fenves AZ, Kirkpatrick HM III, Patel VV, et al. Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. Clin J Am Soc Nephrol. 2006;1:441–7.
Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. Nat Rev Nephrol. 2012;8:589–601.
Kraut JA, Xing SX. Approach to the evaluation of a patient with an increased serum osmolal gap and high-anion gap metabolic acidosis. Am J Kidney Dis. 2011;58:480–4.
Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. Nat Rev Nephrol. 2010;6:274–85.
Liss DB, Paden MS, Schwarz ES, et al. What is the clinical significance of 5-oxoproline (pyroglutamic acid) in high anion gap metabolic acidosis following paracetamol (acetaminophen) exposure? Clin Toxicol. 2013;51:817–27.
Mirrakhopov AE, Barbaryan A, Gray A, et al. The role of renal replacement therapy in the management of pharmacologic poisonings. Int J Nephrol. 2016:3047329, 12 pages
Oh MS, Halperin ML. Toxin-induced metabolic acidosis. In: Jennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 383–415.
Pien K, van Vlem B, van Coster R, et al. An inherited metabolic disorder presenting as ethylene glycol intoxication in a young adult. Am J Forensic Med Pathol. 2002;23:96–100.

Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015;43:461–47.

Schep LJ, Slaughiter RJ, Temple WA, et al. Diethylene glycol poisoning. Clin Toxicol. 2009;47:525–35.

Slaughter RJ, Mason RW, Beasley DM, et al. Isopropanol poisoning. Clin Toxicol. 2014;52:470–8.

Ting SMS, Ching I, Nair H, et al. Early and late presentations of ethylene glycol poisoning. Am J Kidney Dis. 2009;53:1091–7.

Zakharov S, Pelclova D, Diblik P, et al. Long-term visual damage after acute methanol poisonings: longitudinal cross-sectional study in 50 patients. Clin Toxicol. 2015;53:884–92.

Chapter 8
Renal Tubular Acidosis

Renal tubular acidosis (RTA) comprises a group of different renal tubular disorders that are characterized by the inability to excrete H^+ in the urine. As a result, there is a positive H^+ balance, causing metabolic acidosis. The net acid excretion (NAE) is decreased, and some of the patients are unable to lower their urine pH <5.5. Despite severe acidosis, the anion gap (AG) remains normal because the decrease in serum [HCO_3^-] is compensated for by a proportionate increase in serum [Cl^-].

Types of RTAs

Distal RTA was the first one to be described and is, therefore, called type I or classic RTA. It is called distal RTA because the urinary acidification is impaired in the distal segment of the nephron. HCO_3^- loss in the urine is minimal. Subsequently proximal tubular disorder was described and named proximal RTA or type II RTA. In this type, there is HCO_3^- wasting but the distal acidification mechanism is intact. Type III RTA patients share characteristics of both type I and type II and is referred to as incomplete RTA. All these three types have hypokalemia. The term type IV RTA was coined in 1976 to describe patients with hyperchloremic metabolic acidosis, hyperkalemia, hyporeninemia, aldosterone deficiency, and moderate renal insufficiency. These patients were able to acidify their urine (unlike type I patients) and do not have HCO_3^- wasting (unlike type II patients). In 1981, however, a subset of patients with hyperkalemia and metabolic acidosis were unable to acidify their urine. These patients had obstructive uropathy and did not have aldosterone deficiency. They were unable to create a lumen-negative voltage gradient in the cortical collecting duct so that both K^+ and H^+ are not secreted into the lumen. These patients were classified as having voltage-dependent RTA. In order to avoid confusion in terminology, it is better to combine both type IV RTA and voltage-dependent RTA and call "distal RTA with hyperkalemia." Thus, RTA can be classified into the following four types:

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_8

1. Proximal RTA (type II RTA)
2. Distal RTA (classic or type I RTA)
3. Incomplete RTA (type III RTA)
4. Distal RTA with hyperkalemia

In order to understand the various types of RTA, it is important to recapitulate the mechanisms of renal acidification and NAE. As discussed in Chap. 2, HCO_3^- reabsorption and H^+ secretion are important mechanisms to maintain urine pH <5.5 in a normal individual. In order to maintain acid urine, the excretion of HCO_3^- should be minimal, and H^+ secretion should be normal in the urine. This urinary acidification is impaired in most of the conditions of RTAs.

Briefly, reabsorption of HCO_3^- in the proximal tubule occurs because of H^+ secretion into the tubular lumen by Na/H exchanger and H-ATPase. The secreted H^+ combines with the tubular HCO_3^- to form carbonic acid (H_2CO_3), which dissociates into CO_2 and H_2O in the presence of carbonic anhydrase IV. CO_2 diffuses into the cell where it combines with H_2O to form H_2CO_3, which is degraded into H^+ and HCO_3^-. This reaction is catalyzed by carbonic anhydrase II. H^+ is secreted into the lumen, and HCO_3^- is transported into the blood via basolateral Na/HCO_3 cotransporter. Thus, 80% of the HCO_3 is reabsorbed in the proximal tubule (Fig. 2.1).

The remaining 20% of HCO_3^- is reabsorbed (regenerated) in the remaining segments of the nephron. Of these segments, the collecting duct plays an important role in renal acidification. The collecting duct includes the cortical portion and outer and inner medullary segments. This cortical collecting duct contains principal cells and intercalated cells. The latter cells are responsible for acid–base transport. The intercalated cells in the cortical collecting duct are of three types: type A, type B, and type C cells. Type A intercalated cells contain H-ATPase and K/H exchanger in the apical membrane. H^+ that is formed inside the cell from dehydration of H_2CO_3 is secreted into the lumen by these transporters. HCO_3^- exit is facilitated by the Cl/HCO_3 exchanger (Fig. 2.2).

In contrast, type B intercalated cells secrete HCO_3^- into the lumen (Fig. 2.3). These cells possess pendrin, a Cl/HCO_3 exchanger, in the apical membrane and H-ATPase in the basolateral membrane.

Type C (formerly non A, non B) cells express H-ATPase and pendrin (Cl/HCO_3 exchanger) in the apical membrane. These cells also participate in HCO_3^- handling.

The cellular mechanisms of HCO_3^- reabsorption in the cortical collecting duct have been discussed above. The intercalated cells of the outer medullary and inner medullary collecting duct reabsorb HCO_3^- and secrete protons similar to the type A cell mechanisms (Fig. 2.2). The cells of outer medullary and inner medullary collecting duct do not secrete HCO_3^- into the lumen.

Thus, all filtered HCO_3^- is reabsorbed in all segments of the nephron leaving minimal amount in the urine.

Net Acid Excretion

As stated in Chap. 2, the H ions that are generated as fixed acids must be excreted daily in the urine to maintain normal acid–base balance. These H^+ are not excreted as free ions. Instead, they are excreted in the form of titratable acidity (TA) and NH_4^+. Only a small amount of H^+ is excreted as free ions. Each liter of urine contains approximately 0.04 mmol of free H^+. Because of this negligible amount of free H^+, the urine pH is maintained between 4.5 and 6.0. Another reason for the maintenance of acid urine pH is the relatively low concentration of HCO_3^- (<3 mEq/L of urine). Urinary loss of HCO_3^- greater than 5 mEq would generally raise the pH above 6.0 and make the urine alkaline. HCO_3^- loss in the urine is generally equated as a gain of H^+ to the body.

The excretion of H^+ as TA and NH_4^+ is quantified as *net acid excretion* (NAE). NAE is defined as the sum of TA and NH_4^+ minus any H^+ that is added to the body because of urinary loss of HCO_3^-. Therefore, NAE is calculated as follows:

$$\text{NAE} = \text{TA} + \text{NH}_4^+ - \text{HCO}_3^-.$$

In a normal individual, NAE is increased in response to an acid load. Metabolic acidosis increases NAE because the excretion of both TA and NH_4^+ increases. Thus, NAE reflects the amount of H^+ excretion in the form of urinary buffers. Determination of NAE in a patient with hyperchloremic metabolic acidosis can help determine the etiology of this disorder.

NAE is difficult to estimate. However, simple laboratory tests such as urine pH, urine anion gap (U_{AG}), and urine osmolal gap are helpful during the workup of a patient with RTA. Of these three tests, the first two are easy and routinely performed.

Urine pH

- Normal urine pH varies between 4.5 and 6.0, implying appropriate NAE.
- In patients with proximal RTA, urine pH can be acidic or alkaline (see further).
- In patients with distal RTA, urine pH is *always* >6.5.
- In type III RTA, urine pH is >6.5.
- In patients with hyperkalemic RTA (type IV) with aldosterone deficiency, urine pH is usually <5.5.
- In hyperkalemic distal RTA with variable levels of aldosterone, urine pH is *always* >6.5.

Urine Anion Gap (U_{AG})

- U_{AG} ($U_{Na} + U_K - U_{Cl}$) is an indirect measure of NH_4^+ excretion. It is the best measure to distinguish RTA from hyperchloremic metabolic acidosis due to non-renal causes such as chronic diarrhea.
- When $U_{Cl} > (U_{Na} + U_K)$, the U_{AG} is negative, indicating adequate NH_4^+ excretion. On the other hand, when U_{AG} is positive [$U_{Cl} < (U_{Na} + U_K)$], NH_4^+ excretion is decreased.
- In conditions such as diabetic ketoacidosis, Cl^- is excreted mostly with ketoanions than with Na^+, K^+, or NH_4^+; therefore, the U_{AG} becomes falsely positive. Therefore, a direct measurement of NH_4^+ is needed.
- U_{AG} should be determined in patients with urinary $Na^+ > 25$ mEq/L.
- Since direct measurement of NH_4^+ is not available in many clinical laboratories, an indirect measurement can be obtained by calculating the urine osmolal gap.

Urine Osmolal Gap (U_{OG})

- Like serum osmolal gap, U_{OG} is the difference between the measured and calculated urine osmolalities. U_{OG} detects unmeasured anions or cations, and it is an indirect test for NH_4^+ excretion. The U_{OG} is expressed as mOsm/kg H_2O and calculated as follows:

$$U_{OG} = 2\left(Na^+ + K^+\right) + Urea + Glucose\left(all\,in\,mmol/L\right)$$

- Normal U_{OG} values range from 10 to100 mOsm/kg H_2O.
- U_{NH4} excretion is half of U_{OG} due the accompanying anions.
- When U_{OG} is <100 mOsm in metabolic acidosis, it indicates impaired NH_4^+ excretion.
- U_{OG} is thus useful in the differential diagnosis of hyperchloremic metabolic acidosis.

Proximal RTA (Type II RTA)

Definition of Proximal RTA

Proximal RTA is a condition of impaired HCO_3^- reabsorption in the proximal tubule, which is due to a defect in H^+ secretion (decreased activity of either Na/H exchanger or H-ATPase or both), decreased carbonic anhydrase activity, or a defect

in HCO_3^- exit. It can occur as an isolated defect of HCO_3^- reabsorption or in association with other solute defects in the proximal tubule, which is collectively referred to as renal Fanconi syndrome. These characteristics of proximal RTA are given below.

Pathophysiology of Proximal RTA

As discussed above and from Chap. 2 regarding HCO_3^- handling in the kidney, all the filtered HCO_3^- is reabsorbed by the kidney. For example, 4320 mEq (serum [HCO_3^-] 24 × daily GFR 180 L = 4320) of HCO_3^- are filtered daily in a normal individual. All of this HCO_3^- is reabsorbed, and virtually none appears in the urine. Approximately 80% of filtered HCO_3^- is reabsorbed in the proximal tubule. In proximal RTA, HCO_3^- reabsorption is reduced. This results in more HCO_3^- delivery to the distal tubules, and all HCO_3^- not being reabsorbed. This causes loss of HCO_3^- in the urine, and urine pH becomes alkaline (>6.5). This suggests that there is a certain threshold for HCO_3^- reclamation in the proximal tubule in patients with proximal RTA. When the filtered load of HCO_3^- is reduced because of low serum [HCO_3^-] of ~18–20 mEq/L, patients with proximal RTA with normal renal function can reabsorb all HCO_3^-, and urine is free of HCO_3^- with a pH <5.5 (acid). This acidic pH is due to increased NAE, suggesting that distal acidification is intact. Thus, acidification of urine depends on serum [HCO_3^-] in patients with proximal RTA. Table 8.1 explains HCO_3^- handling and urine pH in proximal RTA, which occurs in two phases: initial and steady-state phases.

Table 8.1 Handling of HCO_3^- in normal subjects and patients with proximal RTA

Subjects	Amount (mEq) of filtered HCO_3^-	Amount (mEq) reabsorbed in the proximal tubule	Amount (mEq) delivered to distal segments	Amount (mEq) of HCO_3^- excreted	Urine pH
Normal	4320	3456 (80%)	864 (20%)	<3	<5.5
Proximal RTA					
Initial phase	4320	2808 (65%)	1512 (25%)[a]	1134	>6.5
Steady state	3600[b]	2880 (76%)	864 (24%)	<3	<5.5

[a]Maximum reabsorption
[b]Calculated at serum [HCO_3^-] of 20 mEq/L

Table 8.2 Causes of proximal RTA

Primary (hereditary) causes	Secondary (acquired) causes
Isolated proximal RTA not associated with renal Fanconi syndrome	*Dysproteinemic states*
Genetic	Multiple myeloma
Autosomal recessive	Light-chain deposition disease
Autosomal dominant	Amyloidosis
Sporadic	*Tubulointerstitial diseases*
Carbonic anhydrase (CA) II deficiency	Sjögren's syndrome
CA IV deficiency	Posttransplantation rejection
Proximal RTA associated with renal Fanconi syndrome	Medullary cystic disease
Inherited disorders	*Secondary hyperparathyroidism with chronic hypocalcemia*
Cystinosis	Vitamin D deficiency or resistance
Wilson's disease	Vitamin D dependency
Tyrosinemia	*Others*
Hereditary fructose intolerance	Nephrotic syndrome
Lowe syndrome	Paroxysmal nocturnal hemoglobinuria
Galactosemia	*Drugs*
Dent disease	CA inhibitors (acetazolamide, topiramate)
	Anticancer drugs (ifosfamide, cisplatin, carboplatin, streptozotocin, azacitidine, suramin, mercaptopurine)
	Antibacterial drugs (outdated tetracyclines, aminoglycosides)
	Anticonvulsants (valproic acid, topiramate)
	Antiviral agents (DDI, adefovir, cidofovir, tenofovir)
	Calcineurin inhibitor (tacrolimus)
	Others (fumarate, ranitidine, salicylates, alcohol, cadmium)

Causes of Proximal RTA

Proximal RTA can be either hereditary (primary) or acquired (secondary). As stated, it can occur as an isolated defect in HCO_3^- transport only (called isolated proximal RTA) or in association with multiple tubular transport defects (called renal Fanconi syndrome). Table 8.2 shows the causes of proximal RTA.

Renal Fanconi Syndrome

Definition

It is defined as a proximal tubular dysfunction, leading to excessive urinary excretion of HCO_3^-, glucose, phosphate, uric acid, amino acids, and to a lesser extent Na^+, K^+, and Ca^{2+}.

Pathogenesis

The pathogenesis of renal Fanconi syndrome is not completely understood because several mechanisms may exist, particularly for drug-induced syndrome. However, mitochondrial cytopathy and disruption of cellular energy production as well as impaired proximal tubular endocytosis seem to cause dysfunction of proximal tubule.

Laboratory and Clinical Manifestations

The urinary losses of solutes lead to acidosis, electrolyte abnormalities (hypokalemia, hypophosphatemia, hypouricemia), dehydration with resultant increase in renin-AII-aldosterone production, rickets, osteomalacia, growth, and mental retardation.

Characteristics of Proximal RTA

Based on the above discussion, the characteristics of proximal RTA include the following:

1. Hyperchloremic (non-AG) metabolic acidosis
2. HCO_3^- wasting in early or initial phase when serum [HCO_3^-] is 20 mEq/L and urine pH is usually >6.5
3. Urine pH <5.5 in chronic (steady) phase (serum [HCO_3^-] is <18–20 mEq/L
4. Hypokalemia is extremely common because of excess urinary loss of K^+. This is due to the increased delivery of Na^+ and HCO_3^- to the distal nephron, where Na^+ and K^+ exchange occurs. Also, volume depletion-induced aldosterone may contribute to K^+ wastage
5. Positive U_{AG}
6. Intact distal tubule acidification
7. Abnormalities associated with renal Fanconi syndrome

Causes of Proximal RTA

Table 8.2 shows both genetic and acquired causes of proximal RTA associated with renal Fanconi syndrome. The most common genetic cause of renal Fanconi syndrome is cystinosis in children and adolescents, whereas multiple myeloma and drugs are important causes in adults.

Diagnosis of Proximal RTA

- Suspect proximal RTA in an adult with chronic hyperchloremic metabolic acidosis, hypokalemia, and urine pH <5.5 with serum [HCO_3^-] <20 mEq/L
- Confirmatory tests include:
  1. Positive U_{AG}
  2. Fractional excretion of HCO_3^- >15% (even >5% may be sufficient in some patients)
  3. HCO_3^- titration test (definitive test): a marked increase in urinary excretion of HCO_3^- and pH occurs, as serum [HCO_3^-] is raised to normal levels (i.e., above renal threshold) by i.v. administration of $NaHCO_3$
- Glucosuria in the presence of normal serum glucose levels, phosphaturia, or other solute excretion establishes the diagnosis of renal Fanconi syndrome.
- Growth retardation and rickets in children and osteopenia as well as pseudofractures in adults should alert the physician to consider proximal RTA as one of the diagnoses.

Clinical Manifestations of Proximal RTA

- Skeletal abnormalities and osteomalacia are common due to chronic metabolic acidosis and vitamin D deficiency. Hypophosphatemia may also contribute to skeletal abnormalities.
- Vitamin D deficiency is due to decreased formation of $1,25(OH)_2D_3$ from $25(OH)D_3$, as proximal tubular production of 1α-hydroxylase is reduced.
- Osteopenia and pseudofractures occur in adults.
- Nephrocalcinosis and nephrolithiasis are rather uncommon, except in patients treated for epilepsy with topiramate. This drug inhibits carbonic anhydrase and causes hypercalciuria, hypocitraturia, and alkaline urine pH with resultant formation of calcium phosphate stones.

Specific Causes of Isolated Proximal RTA

Autosomal Recessive Proximal RTA

- Caused by mutations in Na/HCO_3 cotransporter isoform 1 located in the basolateral membrane of the proximal tubule and eyes. Described initially in 2- and 16-year-old females.
- Clinical manifestations include short stature, mental retardation, cataracts, bilateral glaucoma, and band keratopathy. Low HCO_3^-, non-AG acidosis, and acid urine were observed. However, both parents were normal.
- Treatment includes lifelong alkali therapy.

Autosomal Dominant Proximal RTA

- Described only in two brothers belonging to a single Costa Rican family.
- Gene mutation is unknown.
- Clinical manifestations include growth retardation and reduced bone density. Both brothers had low serum [HCO_3^-] with acid urine.
- Treatment is lifelong alkali therapy.

Sporadic Form

- A transient form of inherited proximal RTA, requiring alkali therapy initially, and then discontinuation after several years.

Carbonic Anhydrase (CA) Deficiency

- Two isoforms of CA have been described.
- CA II is cytoplasmic and found in the proximal and distal tubule.
- CA IV is located in the apical membrane of the proximal tubule.
- CA II deficiency is caused by mutations in CA II gene and inherited as an autosomal recessive disease.
- CA II deficiency patients are usually Arabic in origin.
- Early manifestations include growth and mental retardation, osteopetrosis, cerebral calcification, hypokalemia, proximal muscle weakness, and other features of both proximal and distal (type III) RTAs.
- CA IV deficiency impairs HCO_3^- reabsorption in the proximal tubule, but a genetic mutation has not been described.

Specific Causes of Renal Fanconi Syndrome

Cystinosis

- Cystinosis is an important cause of renal Fanconi syndrome in children.
- It is caused by inactivating mutations in CTNS which encodes a lysosomal membrane protein called cystinosin. It is a membrane transporter that is responsible for cystine export from lysosomes.
- Because of this mutation, transport of cystine is impaired, with resultant accumulation of cystine in renal tubules and other organs.
- Nephropathic cystinosis manifests in the first year of life with failure to thrive, increased thirst, polyuria, and hypophosphatemic rickets. Several other nonrenal manifestations can occur in cystinosis.

- Increased urinary loss of Na^+, Ca^{2+}, and Mg^{2+} occurs in cystinosis. Renal calcification is rather common. ESRD occurs by 10 years of age, and cystinosis does not recur in transplanted kidney.
- Specific therapy of renal Fanconi syndrome depends on the underlying cause. Supportive therapy is crucial with replacement of fluids and electrolytes.
- Cysteamine, a cystine-depleting agent, converts cystine into a mixed disulfide cysteamine-cysteine molecule that exits lysosomes via the lysine transporter. This agent has been shown to improve renal function once it is started after the diagnosis of cystinosis is confirmed.

Lowe Syndrome (Oculocerebrorenal Syndrome)

- Lowe syndrome is an X-linked recessive syndrome.
- Characterized by a triad of congenital cataracts, mental retardation, and renal dysfunction.
- Caused by a mutation in the OCRL1 gene that encodes the enzyme phosphatidylinositol 4,5-bisphosphate phosphatase, which localizes in the Golgi complex and involved in protein trafficking.
- Aminoaciduria with sparing of branch-chain amino acids (leucine, isoleucine, proline, and valine) is characteristic of Lowe syndrome.
- Renal function is normal at birth. By 1 year of age, proximal tubular dysfunction and proteinuria are common. Renal histology is characterized by both glomerular and interstitial fibrosis with renal failure during the fourth and fifth decades of life.
- Hypophosphatemic rickets and osteopenia and growth retardation may be seen.
- Treatment is symptomatic and supportive care with replacement of fluids and electrolytes.

Dent Disease

- Dent disease is an X-linked recessive disease with associated renal Fanconi syndrome.
- It is caused by inactivating mutations in the CLCN5 gene, which encodes a renal chloride channel, CLC-5.
- The disease is characterized by varying degrees of low molecular weight proteinuria, hypercalciuria, nephrolithiasis, hyperphosphaturia, and rickets.
- Renal failure gradually develops in patients with Dent disease. Renal biopsy shows chronic tubulointerstitial disease with calcium deposits. Glomeruli are normal.
- Treatment of Dent disease is largely supportive.

Treatment of Proximal RTA

The physician should address the cause of proximal RTA and take appropriate steps to improve acidosis and skeletal abnormalities.

- Alkali therapy is indicated in all the patients (Table 8.3).
- In *children*, the aim is to prevent growth abnormalities. Administration of $NaHCO_3$ or its metabolic equivalent (citrate) to maintain serum [HCO_3^-] to near-normal levels (22–24 mEq/L) is desirable to reestablish normal growth.
- Maintenance of normal serum [HCO_3^-] exacerbates kaliuresis; therefore, high doses of K^+ supplements are necessary.
- Alkali therapy restores growth and volume with suppression of renin-AII-aldosterone system.
- In *adults*, it is not necessary to maintain normal serum [HCO_3^-].
- Adults require between 50 and 100 mEq of alkali daily.
- $NaHCO_3$ and baking soda are inexpensive. Both of them may cause osmotic diarrhea; therefore, small and dividing doses may lower this adverse effect.
- Diuretics such as amiloride may be helpful in some patients by preventing K^+ loss.
- Thiazide and loop diuretics also help in lowering HCO_3^- requirements by volume depletion and increasing HCO_3^- reabsorption in the proximal tubule, but hypokalemia may be aggravated.
- Polycitra-K provides both K and HCO_3 and is recommended by many physicians.
- Active vitamin D_3 and phosphate supplementation help skeletal growth and acidification in patients with low serum phosphate levels.
- Note that citrate increases aluminum absorption.

Table 8.3 Alkali preparations

Preparation	Amount of HCO_3^- or its equivalent
$NaHCO_3$	4 mEq/325 mg tablet or 8 mEq/650 mg tablet
Baking soda ($NaHCO_3$)	60 mEq/teaspoon (4.5 g) of powder
K-Lyte (K^+ HCO_3/K^+ citrate)	25–50 mEq/tablet
Urocit-K (K^+ citrate)	5–10 mEq/tablet
Kaon (K^+ gluconate)	5 mEq/mL or 1.33 mEq/mL
Shohl's solution, Bicitra (Na^+ citrate/citric acid)	1 mEq/mL
Polycitra (Na^+ citrate/K^+ citrate/citric acid)	2 mEq/mL
Polycitra-K (K^+ citrate/citric acid)	2 mEq/mL

Distal (Classic or Type I) RTA

Characteristics of Distal RTA

Distal RTA is characterized by:

1. Hyperchloremic (non-AG) metabolic acidosis
2. Inability to acidify urine despite severe acidosis (urine pH > 6.5)
3. Hypokalemia
4. Positive U_{AG}
5. Skeletal abnormalities
6. Nephrolithiasis and nephrocalcinosis
7. Intact proximal tubule function

Pathophysiology of Distal RTA

The pathophysiology of type I RTA is fairly understood. Two mechanisms seem important in causing hypokalemic distal RTA:

1. Defective H^+ secretion
2. Backleak of H^+

Defective H^+ Secretion Both of the above defects are due to dysfunction of the type A intercalated cell. Recall that acidification of urine occurs by secretion of H^+ via H-ATPase and K/H exchanger. A functional defect in these transport mechanisms results in positive H^+ balance and acidemia. This leads to a decrease in NAE, particularly NH_4^+ excretion, and HCO_3^- wastage with alkaline pH despite severe acidosis.

Patients with distal RTA have low NH_3 secretion, because of the failure to trap NH_3 in the tubular lumen of the collecting duct which has an alkaline pH. Also, secretion of NH_3 is impaired from the medulla due to interstitial disease caused by nephrocalcinosis or hypokalemia. Thus, impaired secretion of NH_3 into the tubular lumen results in decreased NAE and alkaline urine.

Also, a defect in the exit of HCO_3^- via Cl/HCO_3 exchanger (anion exchanger 1 or AE1) results in intracellular alkalinization, which inhibits apical H^+ secretion.

Genetic studies have shown that mutations in B_1 and A_4 subunit of H-ATPase and AE1 cause distal RTA. These genetic defects cause hereditary forms of type I distal RTA (see further).

Backleak of H^+ It is believed that type I RTA is due to altered apical membrane permeability of the type A intercalated cell. An experimental study with amphotericin B has proven this belief. There is no defect in H^+ secretion via H-ATPase transporter. However, the secreted H^+ diffuses back into the cells through the permeable apical membrane. As a result, the luminal pH remains alkaline, and excretion of NAE is substantially decreased.

Causes of Distal RTA

Distal RTA can be either hereditary (primary) or acquired. Table 8.4 shows some important causes of distal RTA. The hereditary forms are rather rare but deserve some discussion. Table 8.5 summarizes genetic abnormalities and clinical manifestations.

Table 8.4 Causes of distal (type I) RTA

Hereditary	*Associated with nephrocalcinosis*
Autosomal dominant	Hyperparathyroidism
Autosomal recessive with deafness	Primary nephrocalcinosis
Autosomal recessive without deafness	Idiopathic hypercalciuria
Acquired	Vitamin D intoxication
Associated with systemic disease	Medullary sponge kidney
Multiple myeloma	*Drugs*
Amyloidosis	Amphotericin B
Systemic lupus erythematosus	Toluene
Sjögren's syndrome	Vanadate
Chronic active hepatitis	Lithium
Primary biliary cirrhosis	Analgesics
Cryoglobulinemia	Cyclamate
Thyroiditis	
Posttransplantation rejection	
Balkan nephropathy	

Table 8.5 Clinical characteristics of hereditary distal RTAs

Form	Genetic defect	Age at onset	Clinical features
Autosomal dominant	Mutations in anion exchanger (AE1 or Cl/HCO_3 exchanger)	Adults	Mild metabolic acidosis
			Mild to moderate hypokalemia
			Mild to moderate bone disease
			Nephrocalcinosis/lithiasis, hypocitraturia, hypercalciuria
			Occasional rickets and osteomalacia
Autosomal recessive with deafness	B1 subunit of H-ATPase	Infancy/ childhood	Severe metabolic acidosis
			Vomiting
			Dehydration
			Growth retardation
			Nephrocalcinosis
			Rickets
			Bilateral sensorineural hearing loss
Autosomal recessive without deafness	A4 subunit of H-ATPase	Infancy/ childhood	Same as above, but without deafness (although late onset hearing loss in some)

Diagnosis of Distal RTA

- Suspect distal RTA in subjects with moderate to severe non-AG metabolic acidosis, hypokalemia, and urine pH >6.5
- Confirmatory urinary acidification tests include:

1. Positive U_{AG}
2. NH_4Cl test: In this test, NH_4Cl (100 mg/kg) is dissolved in water and given orally. Following ingestion, sequential urine samples are collected for pH over a period of 6 h. At the same time, serum [HCO_3^-] before and 3 h after NH_4Cl ingestion is determined to document systemic acidosis. The normal response is a decrease in urine pH <5.5. In patients with distal RTA, the urine pH is always >6.5. All patients must be screened for urinary tract infection, as urine pH with urease-producing organisms is alkaline. This test is contraindicated in patients with liver cirrhosis
3. An alternative test is determination of urine to blood (U-B) pCO_2 difference or gradient. In this test, $NaHCO_3$ (500 mEq/L at 3 mL/min) is infused until bicarbonaturia and urine pH >7.5 ensue. In a normal individual, urine pCO_2 increases above blood pCO_2 by 20–30 mmHg (U-B pCO_2 gradient 20–30 mmHg). This indicates adequate distal H^+ secretion. However, in a subject with distal RTA, this U-B pCO_2 gradient cannot be achieved, indicating defective distal H^+ secretion. One exception is amphotericin B-induced distal RTA. In this condition normal U-B pCO_2 can be achieved

Clinical Characteristics of Hereditary Distal RTAs

As stated above, Table 8.5 summarizes genetic abnormalities and clinical features of hereditary distal RTAs.

Complications of Distal RTA

Hypokalemia

Hypokalemia is very common because of increased Na/K cotransporter activity in the distal nephron. Also, dysfunction of H/K-ATPase may contribute to hypokalemia, as inhibition of this transporter by vanadate causes hypokalemic distal RTA. Loss of Na^+ and HCO_3^- in the urine causes volume depletion, which stimulates the renin-AII-aldosterone system and hypokalemia.

Nephrocalcinosis and Nephrolithiasis

One of the major complications of distal RTA is the development of nephrocalcinosis and nephrolithiasis. The mechanisms are as follows:

1. Chronic metabolic acidosis causes bone buffering and dissolution of bone minerals, resulting in high Ca^{2+} excretion
2. In addition, luminal alkalinization inhibits Ca^{2+} reabsorption, promoting an even more excretion of Ca^{2+}
3. Because of high urine pH, solubility of calcium phosphate stones is decreased, thereby causing their formation and precipitation
4. Citrate excretion is reduced in metabolic acidosis, resulting in reduced chelation of free Ca^{2+}

Treatment of Distal RTA

- Treatment in adults is aimed at the correction of primary disease or eliminating the drug that causes distal RTA. Correction of acidosis and hypokalemia should promptly be addressed. Alkali therapy is indicated in all patients.
- $NaHCO_3$ or citrate at 1–1.5 mEq/kg is needed daily. Correction of acidosis reduces K^+ wasting, and therefore, does not require K^+ supplementation. However, some patients may lose K^+. For such patients, K-citrate corrects hypokalemia.
- One disadvantage of above alkalinizing agents is large amount of pill burden, particularly in children. Recently, FDA cleared a drug called ADV7103 for pivotal clinical phase 3 trial for distal RTA. ADV7103 is a prolonged release granule formulation of K-citrate and K bicarbonate used twice daily. A preliminary study in 30 adult and pediatric patients with distal RTA showed serum HCO_3^- levels above 21 mEq/L in 79% of the patients after 6 months of treatment. Although the results are encouraging, more data are required before the drug is used routinely.
- Another agent which has been shown to improve serum HCO_3^- level in CKD patients is TRC101. It is a sodium-free nonabsorbed HCl binder, which was found to increase serum HCO_3^- level from 3.2 to 3.9 mEq/L from baseline in CKD patients with a mean eGFR of 35 mL/min. TRC101 is not an exchange resin like kayexalate or cholestyramine; therefore, there are no changes in Na^+, K^+, Ca^{2+}, or Mg^{2+}. This drug may play an important role in patients with distal RTA.
- Patients with severe acidosis and muscle paralysis due to hypokalemia require i.v. administration.

- Correction of acidosis and hypokalemia improves growth, prevents osteomalacia in adults and rickets in children, hypercalciuria, and nephrocalcinosis as well as nephrolithiasis by improving citrate excretion.

Toluene Ingestion and Distal RTA

- Toluene ingestion causes a high AG metabolic acidosis, if its metabolites (hippuric acid and benzoic acid) are not excreted rapidly due to volume depletion and renal failure.
- When volume is adequate and renal function is normal, these acids are rapidly excreted, and a hyperchloremic metabolic acidosis with hypokalemia develops.
- Possible mechanism includes inhibition of H^+ secretion in the distal tubule.
- Treatment is supportive with volume expansion and $NaHCO_3$ therapy. Dialysis is indicated when severe acidosis and renal failure are present.

Incomplete (Type III) RTA

Type III RTA is characterized by both proximal and distal RTA. Patients with this form of RTA have $HCO3^-$ wastage and inability to acidify their urine <5.5. Generally, the acidification defect is confirmed by one of the urinary acidification tests described earlier.

Clinical characteristics include only mild hyperchloremic metabolic acidosis with near-normal NH_4^+ excretion. They may have low citrate excretion because of increased proximal tubule reabsorption and subsequent development of calcium phosphate stones. Conditions that are associated with type III RTA are chronic tubulointerstitial disease, lithium therapy, and medullary sponge kidney. Genetic deficiency of CA II also causes type III RTA.

Distal RTA with Hyperkalemia

Based on the urinary acidification, distal RTA with hyperkalemia can be divided into two subtypes:

1. Hyperkalemic distal RTA (type IV) with urine pH <5.5
2. Hyperkalemic distal RTA with urine pH >5.5 (also called voltage-dependent RTA)

Both subtypes share the following characteristics:

1. More common in adults than in children
2. Hyperkalemic hyperchloremic metabolic acidosis
3. Inhibition of NH_3 synthesis by hyperkalemia in the proximal tubule
4. Decreased urinary NH_4^+ excretion
5. Absence of nephrocalcinosis and nephrolithiasis

Hyperkalemic Distal RTA (Type IV) with Urine pH <5.5

- Patients with type IV RTA have hyperchloremic metabolic acidosis with urine pH <5.5, suggesting decreased NH_4^+ excretion rather than defective H^+ secretion.
- Patients have selective aldosterone deficiency alone.
- Hyporeninemic hypoaldosteronism is also present in some patients.
- NH_3 synthesis is suppressed by both hyperkalemia and aldosterone deficiency.
- Typically seen in patients with diabetes, who have low renin and aldosterone (hyporeninemic hypoaldosteronism).
- Several drugs that interfere with renin and aldosterone system also cause type IV RTA (Table 8.6).
- Mild to moderate renal impairment.

Hyperkalemic Distal RTA with Urine pH >5.5 (Voltage-Dependent RTA)

- Patients with this form of RTA have hyperkalemic hyperchloremic metabolic acidosis.
- However, these patients cannot lower their urine pH below 5.5.
- The major mechanism includes the inability to maintain lumen negativity (voltage gradient) in the cortical collecting duct. Normally, Na^+ reabsorption occurs via the epithelial sodium channel (ENaC) to maintain favorable voltage gradient for K^- and H^+ secretion into the lumen. When a defect occurs in Na^+ reabsorption, both K^+ and H^+ are not secreted, resulting in hyperkalemia and inability to acidify urine pH below 5.5.
- Obstructive nephropathy is an important cause of voltage-dependent RTA.
- Also, voltage-dependent RTA has been demonstrated by amiloride, which inhibits ENaC.
- Aldosterone levels may be normal, low, or high, but in most cases, reduced levels have been observed.
- Unlike patients with selective aldosterone deficiency or resistance, many patients with voltage-dependent RTA may have normal renal function.

Causes of Both Types of Hyperkalemic Distal RTAs

- Causes of distal RTA with hyperkalemia can be due to systemic diseases, acquired or genetic.
- Mechanisms include selective aldosterone deficiency, hyporeninemic hypoaldosteronism, aldosterone resistance, and drug-induced hypoaldosteronisms (Table 8.6).

Table 8.6 Some causes of distal RTA with hyperkalemia

Hyperkalemic distal RTA (type IV) with urine pH <5.5	Hyperkalemic distal RTA with urine pH >5.5
Primary mineralocorticoid deficiency	*Diseases with both tubulointerstitial and glomerular diseases*
Combined aldosterone and cortisol deficiency	Obstructive nephropathy
Addison's disease	Sickle cell disease
Bilateral adrenal destruction (hemorrhage, surgery, or cancer)	Lupus nephritis
21-hydroxylase deficiency	Kidney transplant rejection
Selective aldosterone deficiency	*Drugs*
Idiopathic hypoaldosteronism	ENaC inhibitors
Heparin use in normal and critically ill patients	Amiloride
Primary mineralocorticoid deficiency with hyporeninemic hypoaldosteronism	Trimethoprim
Diabetes mellitus	Pentamidine
Tubulointerstitial diseases	Triamterene
HIV	Na/K-ATPase inhibitors
Nephrosclerosis	Cyclosporine
Drugs causing low renin and low aldosterone	Tacrolimus
NSAIDs	Aldosterone blockers
β-blockers	Spironolactone
Cyclosporine	Eplerenone
Tacrolimus	*Mineralocorticoid resistance and voltage gradient defect*
Drugs causing high renin and low aldosterone	Pseudohypoaldosteronism type I
ACE-inhibitors	Pseudohypoaldosteronism type II
Angiotensin II receptor blockers	
Ketoconazole	
Heparin	

Diagnosis of Hyperkalemic Distal RTAs

- Diagnosis of hyperkalemic distal RTA is made on the following observations:

  1. An adult (40–70 years) with hyperchloremic metabolic acidosis and hyperkalemia (K^+ = 5.5–6.5 mEq/L)
  2. Hyperkalemia is asymptomatic in many, but some patients may have muscle weakness or cardiac arrhythmia
  3. Serum [HCO_3^-] between 18 and 21 mEq/L
  4. Decreased NAE
  5. Estimation of NH_4^+ excretion using U_{AG}
  6. Mild to moderate renal impairment.
  7. Urine pH either <5.5 or >5.5 (based on etiology)

8. Positive U_{AG}
9. Low fractional excretion of K^+

- If clinical diagnosis could not be made on history and laboratory tests, furosemide or bumetanide test can be performed. Loop diuretics deliver more NaCl to the collecting duct, causing Na^+ reabsorption (via ENaC) and K^+ and H^+ secretion into the lumen. This results in the acidification of urine. Amiloride can obliterate these changes.
- Furosemide test: 40–80 mg of furosemide or 1–2 mg of bumetanide is given orally after collecting a urine sample. Urine samples are collected every hour for 4 h. Normal individuals and selective aldosterone deficiency patients lower their urine pH <5.5. Patients with a defect in voltage gradient cannot lower urine pH <5.5.
- Figure 8.1 shows an approach to the patient with hyperkalemic distal RTA.

Treatment of Hyperkalemic Distal RTAs

- Inquire about dietary and drug history.
- Review the contributing or precipitating factors, such as hyperglycemia, degree of renal dysfunction, or ingestion of salt substitutes.

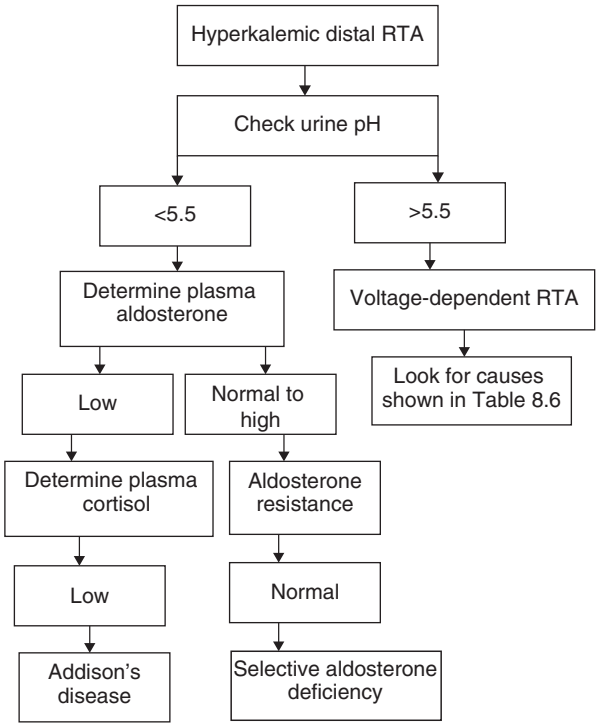

Fig. 8.1 Approach to the patient with hyperkalemic distal RTA

- Pharmacologic treatment should be individualized, and decision depends on the severity of hyperkalemia and acidosis after discontinuation of drugs and appropriate management of associated clinical abnormalities.
- Kayexalate (sodium polystyrene sulfonate) for hyperkalemia (rule out any GI abnormalities before administration).
- Patiromer (8.4 g mixed with water) or sodium zirconium or lokelma (10 g once daily) can be given, if kayexalate is contraindicated or unable to tolerate.
- Liberalization of salt intake in patients with euvolemia.
- Furosemide or bumetanide to improve hyperkalemia.
- Fludrocortisone alone or in combination with furosemide in patients with low aldosterone levels and normal fluid volume status.
- $NaHCO_3$ or Na citrate to improve acidosis.
- NaCl supplement for patients with pseudohypoparathyroidism type 1.
- Hydrochlorothiazide for patients with pseudohypoparathyroidism type 2.

Distinguishing Features of Various RTAs

So far we have discussed various forms of RTAs. However, it is important to remember the similarities and differences among these RTAs for their easy recognition. Table 8.7 summarizes similarities and differences of these RTAs.

Table 8.7 Comparison of clinical findings among various RTAs

Finding	Proximal RTA	Classic distal RTA	Hyperkalemic RTAs
Serum [K^+]	↓	↓	↑
Urine pH with severe acidosis	<5.5	>5.5	<5.5 (aldosterone deficiency) >5.5 (voltage gradient defect)
Urine acidification	N	↓	↓
NH_4^+ excretion	N	↓	↓
U_{AG}	+(or −)	+	+
Fanconi syndrome	Yes	No	No
U-B pCO_2	Normal	↓	↓
Hypercalciuria	No	Yes	No
Nephrocalcinosis/lithiasis	No	Yes	No
Citrate excretion	N	↓	N
Bone lesions	Yes	Yes	No
Renal insufficiency	No	No	Yes
Response to alkali therapy	Less	Good	Yes
			Variable

N normal, ↑ increase, ↓ decrease, + positive

An Approach to the Patient with RTA

Once RTA is suspected based on hyperchloremic (non-AG) metabolic acidosis with low or high serum K^+ levels, the U_{AG} and urine pH are extremely helpful to distinguish diarrhea from hypokalemic RTA. U_{AG} is negative in diarrhea, whereas it is positive in RTA. Once diarrhea is ruled out, the following algorithm (Fig. 8.2) can be used to make the diagnosis of various types of RTAs.

Study Questions

Case 1 An 18-year-old woman with history of systemic lupus erythematosus (SLE) is admitted to the hospital for worsening weakness and problems with breathing for the last 2 weeks. She loves ice cream since childhood. She states that she had 4–6

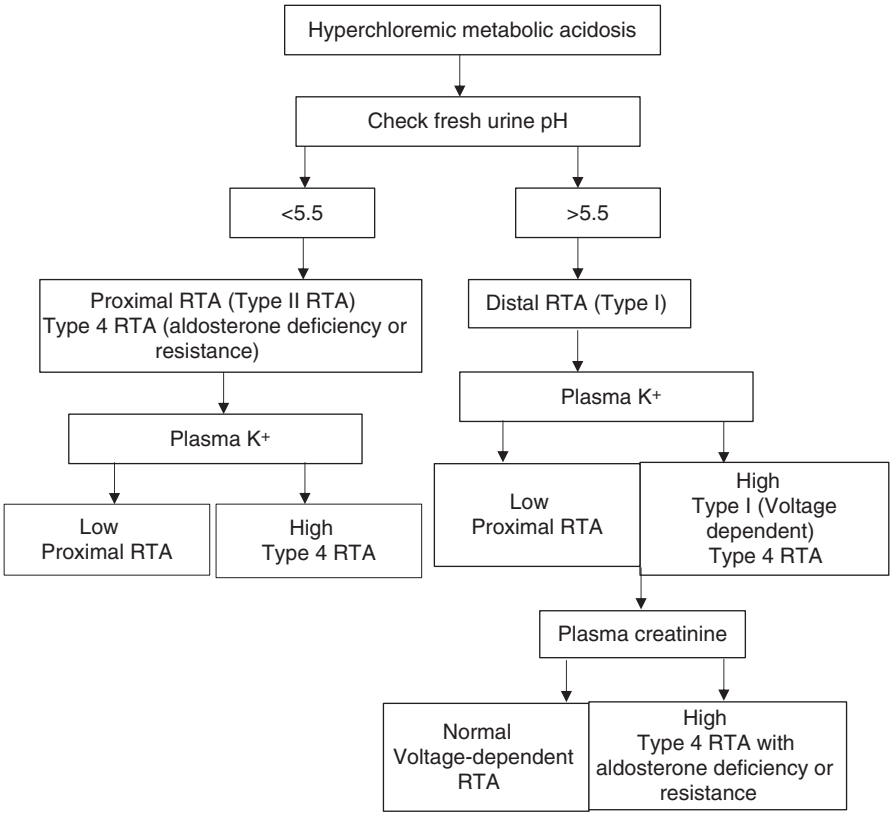

Fig. 8.2 Diagnostic approach to RTAs

urinary tract infections (UTIs) in recent years, which were treated. She is not on any medications. Admitting laboratory values are:

Serum	Urine
Na^+ = 138 mEq/L	pH = 6.6
K^+ = 1.2 mEq/L	Glucose = negative
Cl^- = 118 meq/L	Blood = positive (had recent menstruation)
HCO_3^- = 12 mEq/L	Ketones = negative
Creatinine = 0.6 mg/dL	Protein = 3+
BUN = 22 mg/dL	Na^+ = 60 mEq/L
Glucose = 90 mg/dL	K^+ = 100 mEq/L
ANA = positive	Cl^- = 110 mEq/L
Complement = low	
ABG: pH 7.2, pCO_2 26 mmHg, HCO_3^- 11 mEq/L	

Question 1 Which one of the following is the MOST likely cause of her symptoms?

A. Exacerbation of SLE
B. Proximal RTA
C. Distal RTA
D. Type IV RTA
E. Hypokalemic periodic paralysis

The answer is C. The patient's weakness and respiratory distress are related to hypokalemia rather than exacerbation of SLE. Although glomerular disease is common in SLE, tubular dysfunction is uncommon in the presence of normal renal function. However, hypokalemia-related clinical manifestations have been described prior to the diagnosis of SLE. The serum and urine findings in this patient are suggestive of distal RTA (hyperchloremic metabolic acidosis and alkaline urine pH despite acidosis). A few cases of distal RTA have been reported in the literature. The pathophysiology of distal RTA in lupus patients is unclear; however, destruction of distal nephron by immunoglobulins has been suggested. Proximal RTA in this patient is unlikely as she has no manifestations of Fanconi syndrome. Also, patients with proximal RTA can acidify their urine at a serum [HCO_3^-] of 12 mEq/L. Although type IV RTA has been described in lupus patients, hypokalemia rules out this diagnosis in this patient. Hypokalemic periodic paralysis is also unlikely because of positive ANA, lupus nephritis, and urine [K^+] of 100 mEq/L. In hypokalemic periodic paralysis, urine K^+ is low because of transcellular distribution.

Question 2 Is urine anion gap (U_{AG}) helpful in this patient?

Answer Yes. Calculation of U_{AG} is helpful in the differential diagnosis of hyperchloremic metabolic acidosis. In this patient, the U_{AG} is positive, ruling out diarrhea as a cause of her hyperchloremic metabolic acidosis.

Question 3 Does she require workup for nephrocalcinosis/lithiasis?

Answer Yes. She had several UTIs in the past. Although frequent UTIs are common in young females, she requires minimum workup for nephrocalcinosis/lithiasis as a cause of her UTIs. Patients with distal RTA frequently develop nephrocalcinosis/lithiasis.

Case 2 A 19-year-old thin female student is brought to the Emergency Department by her friends for altered mental status, euphoria, and dizziness after a rave party. She has no history of drug abuse, and is not on any medications. Physical examination is normal except for a blood pressure of 90/60 mmHg with pulse rate of 102 beats/min. Laboratory results on admission and 18 h later are:

On admission	18 h later
Na^+ = 142 mEq/L	Na^+ = 138 mEq/L
K^+ = 3.5 mEq/L	K^+ = 2.2 mEq/L
Cl^- = 100 meq/L	Cl^- = 118 meq/L
HCO_3^- = 12 mEq/L	HCO_3^- = 14 mEq/L
Creatinine = 1.8 mg/dL	Creatinine = 0.9 mg/dL
BUN = 22 mg/dL	BUN = 12 mg/dL
Glucose = 96 mg/dL	Glucose = 100 mg/dL
ABG: pH 7.24, pCO_2 28 mmHg, HCO_3^- 11 mEq/L	ABG: pH 7.31, pCO_2 29 mmHg, HCO_3^- 13 mEq/L
Urine pH = 5.2	Urine pH = 6.5

Question 1 Characterize the acid–base disorder on admission and 18 h later.

Answer On admission, she has a high AG metabolic acidosis with appropriate respiratory compensation, and 18 h later, the acid–base disorder is hypokalemic hyperchloremic metabolic acidosis and respiratory compensation is appropriate.

Question 2 Which one of the following agents causes these types of acid–base disorders?

A. Topiramate
B. Ifosfamide
C. Toluene
D. Cisplatin
E. Tenofovir

The answer is C. Toluene is initially metabolized to hippurate, which causes a high AG metabolic acidosis. Subsequently, hippurate is rapidly excreted in the urine with volume expansion, and the AG disappears. The typical acid–base disorder is hyperchloremic metabolic acidosis with severe hypokalemia. Hypokalemia is related to more distal delivery of Na^+ with hippurate, leaving Cl^- behind. Some of

the patients are unable to acidify their urine due to impaired H^+ secretion. All other drugs cause proximal RTA with adequate urinary acidification once serum [HCO_3^-] is below 18 mEq/L.

Case 3 A 34-year-old man, brought to the Emergency Department by his friend, complains of weakness, fatigue, poor appetite, and dizziness for 2 weeks. He has not seen any physician for 5 years. Other than daily cocaine use, he has no significant medical history. He is not on any prescription medications. Physical examination reveals orthostatic blood pressure and pulse changes. Except for anal condyloma acumunata, the remaining examination is unremarkable. Rapid HIV test is positive. Laboratory values on admission:

Serum	Urine
Na^+ = 126 mEq/L	pH = 5.2
K^+ = 6.5 mEq/L	Glucose = negative
Cl^- = 110 meq/L	Blood = negative
HCO_3^- = 13 mEq/L	Protein = negative
Creatinine = 2.1 mg/dL	Na^+ = 101 mEq/L
BUN = 42 mg/dL	K^+ = 30 mEq/L
Glucose = 60 mg/dL	Cl^- = 40 mEq/L
ABG: pH 7.29, pCO_2 28 mmHg, HCO_3^- 12 mEq/L	

Question 1 What is the acid–base disorder?

Answer Hyperkalemic hyperchloremic (non-AG) metabolic acidosis with appropriate respiratory compensation.

Question 2 Which one of the following is the correct diagnosis?

A. Proximal RTA (type II)
B. Distal RTA (type I)
C. Incomplete RTA (type III)
D. Type IV RTA with hypoaldosteronism
E. Hyperkalemic RTA with a defect in voltage gradient

The answer is D. Serum and urine chemistry and orthostatic changes suggest Addison's disease, which causes type IV RTA. Hypoaldosteronism due to adrenal gland destruction by viruses (HIV, CMV), bacteria (mycobacterium tuberculosis), or fungal agents has been described. Patients with type IV RTA due to aldosterone deficiency can acidify their urine.

Proximal RTA is unlikely because of hyponatremia and hyperkalemia. Note that the patients with proximal RTA can acidify their urine at this level of serum [HCO_3^-], as all of this HCO_3^- can be reabsorbed and generate an acid urine.

Patients with incomplete RTA cannot acidy their urine even after an acid load. Also, hyperkalemic distal RTA patients with a defect in voltage gradient cannot acidify their urine. Therefore, options A, B, C, and E are incorrect.

Case 4 A 42-year-old man presents to his primary care physician for left flank pain and hematuria. Urinalysis reveals a pH of 6.9 and hematuria only. There is no evidence of UTI. Renal ultrasound shows the presence of kidney stones. He has no deafness. Serum chemistry and ABG show mild hypokalemic hyperchloremic metabolic acidosis. Serum creatinine is normal. He has a family history of kidney stones, and several members have mild hypokalemic hyperchloremic metabolic acidosis.

Question 1 Which one of the following RTAs is the MOST likely diagnosis?

A. Proximal RTA
B. Distal RTA
C. Type IV RTA with aldosterone deficiency
D. Incomplete RTA
E. Hyperkalemic RTA with inability to acidy urine

The answer is B. This patient has hereditary form of distal RTA with autosomal dominant inheritance. It occurs in adults; autosomal recessive forms are diagnosed in infancy and childhood with or without deafness. Hyperkalemic RTA with a defect in voltage gradient is seen in patients with mild to moderate renal dysfunction. Type IV RTA patients with aldosterone deficiency have mild renal impairment and can acidify their urine. Patients with incomplete RTA may have a combination of both proximal and distal RTA. They may present with acid urine, but the diagnosis is established only after an acid load. Proximal RTA patients present with severe hypokalemia, but nephrolithiasis is uncommon. Thus, options A, C, D, and E are incorrect.

Question 2 What is the genetic defect in this patient?

A. Mutations in the gene encoding Cl/HCO_3 exchanger (anion exchanger 1, AE1)
B. Mutations in the gene encoding B1 subunit of H-ATPase
C. Mutations in the gene encoding a4 subunit of H-ATPase
D. Mutations in the gene encoding carbonic anhydrase II (CA II) enzyme
E. Deficiency of Na/H exchanger (NHE3)

The answer is A. Autosomal dominant distal RTA is caused by mutations in the gene encoding the basolateral Cl/HCO_3 exchanger. They are unable to acidify their urine. They have mild hypokalemia and mild hyperchloremic acidosis. They have hypercalciuria with hypocitraturia with development of nephrocalcinosis/lithiasis later in life.

Gene mutations stated in options B and D cause autosomal recessive distal RTA with or without deafness, respectively. Deficiency of CA II enzyme causes distal RTA with osteopetrosis and cerebral calcifications. It occurs mostly in Arab populations of the Middle East. At times patients present with clinical manifestations of both proximal and distal RTA. Deficiency of Na/H exchanger causes possibly autosomal dominant form of proximal RTA, and so far no gene mutations have been reported. Thus, options B, C, D, and E are incorrect.

Case 5 A 32-year-old woman with seizure disorder and migraine is consulted for hyperchloremic metabolic acidosis with serum [HCO_3^-] of 19 mEq/L. Her urine pH is 6.4.

Question 1 Which one of the following medications causes this acid–base disorder?

A. Phenytoin
B. Topiramate
C. Levetiracetam
D. Carbamazepine
E. Gabapentin

The answer is B. Except for topiramate, all other drugs are not known to cause hyperchloremic metabolic acidosis. Topiramate is a neuromodulator that is approved for use in the treatment of seizure activity and for migraine prophylaxis. Initially, it was observed that topiramate causes type II RTA and hyperchloremic metabolic acidosis in children. Since then, a number of case reports in adults have been described. Discontinuation of the drug improves serum [HCO_3^-] with resolution of RTA.

Question 2 Why is her urine pH alkaline?

Answer Topiramate is an inhibitor of carbonic anhydrase, causing HCO_3^- loss in the urine. This results in alkaline urine pH.

Case 6 A 65-year-old woman with type 2 diabetes is referred to by a primary care physician for evaluation of hyperkalemia. Other than hypertension, she has no significant medical history. Her medications include hydrochlorothiazide 25 mg QD, sitagliptin 50 mg QD, glipizide 5 mg QD, and lisinopril 20 mg QD. Her blood pressure is 144/84 mmHg with a pulse rate of 82 beats/min. She has a trace pedal edema. The rest of the examination is normal. Recent laboratory results:

Serum	Urine
Na^+ = 136 mEq/L	pH = 5.4
K^+ = 6.1 mEq/L	Glucose = negative
Cl^- = 110 meq/L	Blood = negative
HCO_3^- = 19 mEq/L	Protein = 2+
Creatinine = 1.9 mg/dL (eGFR = 49 mL/min)	Protein/creatinine ratio = 1
BUN = 22 mg/dL	Na^+ = 80 mEq/L
Glucose = 120 mg/dL	K^+ = 30 mEq/L
A1c = 7.9%	Cl^- = 60 mEq/L

Table 8.8 Clinical features of hyporeninemic hypoaldosteronism

Feature	Approximate prevalence
Age (yr)	~65
Presence of diabetes	50%
Hyperkalemia	75%
eGFR	50 mL/min
Type IV RTA	>50%
Serum [HCO_3^-]	18–22 mEq/L
Serum [HCO_3^-] < 13 mEq/L	0
Hypertension	75%
Congestive heart failure	50%
Arrhythmias	24%

Question 1 What is the reason for her hyperkalemia with eGFR of 49 mL/min?

Answer Hyperkalemia is disproportionate to her renal dysfunction. From several studies, it is clear that diabetic patients develop hyperkalemia due to hyporeninemic hypoaldosteronism. In this patient, lisinopril, an ACE-I, can raise renin levels, but her aldosterone levels can be low. Table 8.8 shows some clinical features of hyporeninemic hypoaldosteronism.

Question 2 What is your suggestion for the management of her hyperkalemia?

Answer As stated before, type IV RTA can be managed by several ways. In this patient, switching diuretic to furosemide (discontinuation of hydrochlorothiazide) and restricting K^+ in diet may be sufficient to manage hyperkalemia. Also, better control of glucose (A1c 7–7.5%) and blood pressure is necessary.

Case 7 A 44-year-old woman with Sjögren's syndrome with hypergammaglobulinemia and tubulointerstitial disease is referred to renal clinic for evaluation of documented hypokalemic hyperchloremic metabolic acidosis. She was treated with corticosteroids for tubulointerstitial disease. Her serum [HCO_3^-] is 16 mEq/L and eGFR is 56 mL/min. Serum phosphate, uric acid, and glucose levels are normal.

Question 1 What other pertinent lab test you order at this time?

A. Arterial blood gas
B. Renal biopsy to know the extent of interstitial disease
C. Urinalysis
D. Serum renin and aldosterone levels
E. None

The answer is C. It is important to know whether the patient is able to acidify or alkalinize her urine. Patients with Sjögren's syndrome can develop type I or type II RTA. At times, they can present with both type I and type II RTAs. Urine pH is an

important determinant in the diagnosis of the type of RTA. One large study reported that 73% of their patients with Sjögren's syndrome and renal disease developed RTA and the predominant type was type I RTA. All other tests are not important at this time.

Question 2 When urine pH is 6.8, what type of RTA does this patient have?

Answer Classic distal RTA (type I). Proximal or type II RTA patients can acidify their urine at serum [HCO_3^-] of 16 mEq/L because all this HCO_3^- can be reabsorbed, and the urine pH will be acidic.

Question 3 What is the mechanism of classic distal RTA in patients with Sjögren's syndrome?

Answer To my knowledge, there are two case reports that showed absence of H-ATPase in the cortical collecting duct on renal biopsies in these patients. This suggests that patients with Sjögren's syndrome are unable to secrete H^+ and acidify their urine.

Case 8 Which one of the following statements is TRUE regarding distal RTA?

A. Inability to acidify urine
B. Prone to develop calcium phosphate stones
C. Urinary citrate excretion is low
D. Urinary NH_4^+ excretion is low
E. All of the above

The answer is E. All of the above statements are correct. Thus, answer E is correct. Of particular importance is the development of calcium phosphate stones because calcium phosphate is soluble in alkaline pH and can precipitate in renal tubules. On the other hand, calcium oxalate stones are formed in acidic pH.

Case 9 Match the following causes with their RTAs:

Cause	RTA
A. Obstructive uropathy	1. Classic distal RTA
B. Spironolactone	2. Hyperkalemic distal RTA with alkaline urine
C. Valproic acid	3. Type IV RTA with acid urine
D. Ifosfamide	4. Proximal RTA
E. Amiloride	
F. Cyclosporine	
G. NSAIDs	
H. Medullary sponge kidney	

Answers A = 2; B = 3; C = 4; D = 4; E = 2; F = 1; G = 3; H = 1.

Suggested Reading

Alexander RT, Bitzan M. Renal tubular acidosis. Pediatr Clin North Am. 2019;66:135–57.
Bockenhauer D, Kleta R. Approach to the patient with renal Fanconi syndrome, glycosuria, or aminoaciduria. In: Turner N, Lameire N, Goldsmith DJ, et al., editors. Oxford textbook of clinical nephrology. 4th ed. Oxford: Oxford University Press; 2016. p. 412–21.
Basu G, Sudhakar G, Mohapatra A. Renal tubular acidosis. Clin Quer Nephrol. 2013;2:166–78.
Batlle D, Arruda J. Hyperkalemic forms of renal tubular acidosis: Clinical and pathophysiological aspects. Adv Chronic Kidney Dis. 2018;25:321–33.
Batlle D, Haque SK. Genetic causes and mechanisms of distal renal tubular acidosis. Nephrol Dial Transplant. 2012;27:3691–704.
Bertholet-Thomas A, Guittet C, Manso MA, et al. Safety and efficacy of ADV7103, an innovative prolonged-release oral alkalizing combination product, after 6-months of treatment in distal renal tubular acidosis (dRTA) patients. 2017; ASN/Kidney week (Abstract).
Bushinsky DA, Hostetter T, Klaerner G, et al. Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. Clin J Am Soc Nephrol. 2018;13:26–35.
Gil-Peña H, Mejia M, Santos F. Renal tubular acidosis. J Pediatr. 2014;164:691–8.
Golembiewska E, Ciechanowski K. Renal tubular acidosis-underrated problem? Acta Biochim Pol. 2012;59:213–7.
Goldfarb DS. Refining diagnostic approaches in nephrolithiasis. Incomplete distal renal tubular acidosis. Clin J Am Soc Nephrol. 2017;12:1380–2.
Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. QJ Med. 2014;107: 261–9.
Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. Nephrol Dial Transplant. 2012;27:4273–87.
Izzedine H, Launay-Vacher V, Isnard-Bagnis C, et al. Drug-induced Fanconi syndrome. Am J Kidney Dis. 2003;41:292–309.
Karet FE. Mechanisms in hyperkalemic renal tubular acidosis. J Am Soc Nephrol. 2009;20:251–4.
Klootwijk ED, Reihold M, Unwin RJ, et al. Renal Fanconi syndrome: taking a proximal look at the nephron. Nephrol Dial Transplant. 2015;30:1456–60.
Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. Nat Rev Nephrol. 2012;8:589–601.
Kurschat CE, Alper SP. Hereditary renal tubular acidosis. In: Mount DB, Pollak MR, editors. Molecular and genetic basis of renal disease. A companion to Brenne & Rector's the kidney. Philadelphia: W.B. Saunders, Inc.; 2008. p. 269–94.
Kwon CY, Mount DB. Hereditary disorders of the proximal tubule. In: Mount DB, Pollak MR, editors. Molecular and genetic basis of renal disease. A companion to Brenne & Rector's the kidney. Philadelphia: W.B. Saunders, Inc.; 2008. p. 201–27.
Laing CM, Toye AM, Capasso G, et al. Renal tubular acidosis: developments in our understanding of the molecular basis. Int Natl J Biochem Cell Biol. 2005;37:1151–61.
Moorthi KMLST, Batlle D. Renal tubular acidosis. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 417–67.
Reddy P. Clinical approach to renal tubular acidosis in adult patients. Int J Clin Pract. 2011;65:350–60.
Rodriguez-Soriano J. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol. 2002;13:2160–70.
Soleimani M, Rastegar A. Pathophysiology of renal tubular acidosis: core curriculum 2016. Am J Kidney Dis. 2016;68:488–98.
Trepiccione F, Prosperi F, Rosenburch de la Motte L, et al. New findings on the pathogenesis of distal renal tubular acidosis. Kidney Dis. 2017;3:98–105.
Vallès PG, Batlle D. Hypokalemic distal renal tubular acidosis. Adv Chronic Kidney Dis. 2018;25:303–20.

Chapter 9
Acid–Base Disorders in Gastrointestinal Diseases

In the previous chapter, we discussed both hypo- and hyperkalemic hyperchloremic (non-anion gap) metabolic acidoses due to renal causes. There are several other nonrenal causes for hypokalemic hyperchloremic metabolic acidosis. The most important nonrenal cause is gastrointestinal (GI) disorder and certain medications that are handled by the GI tract. Table 9.1 shows GI causes of acid–base disorders. This chapter deals only with hyperchloremic metabolic acidosis caused by GI disorders. D-lactic acidosis due to short bowel syndrome was discussed in Chap. 5.

Before we discuss the pathophysiology of hyperchloremic metabolic acidosis, it is essential to understand water and electrolyte handling by the GI tract.

Water Handling

Figure 9.1 illustrates approximate daily water handling by the GI tract following a meal, which is summarized as follows:

- Daily intake of water from diet and drinking amounts to 2 L.
- Secretions from the saliva, stomach, bile, pancreas, and small intestine amount to 7 L.

Table 9.1 Major acid–base disorders of GI origin

Hyperchloremic metabolic acidosis	Metabolic alkalosis
Diarrhea	Vomiting
Biliary fistula	Nasogastric suction
Pancreatic fistula	Psychogenic vomiting
Villous adenoma	Gastrostomy drainage
Ureterosigmoidostomy	Congenital chloridorrhea
Ureterojejunostomy	Ulcerative colitis
Ureteroileostomy	Crohn's disease
Laxatives	Villous adenoma
Cholestyramine	Calcium (milk)-alkali syndrome
Short bowel syndrome (D-lactic acidosis)	Antacids

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_9

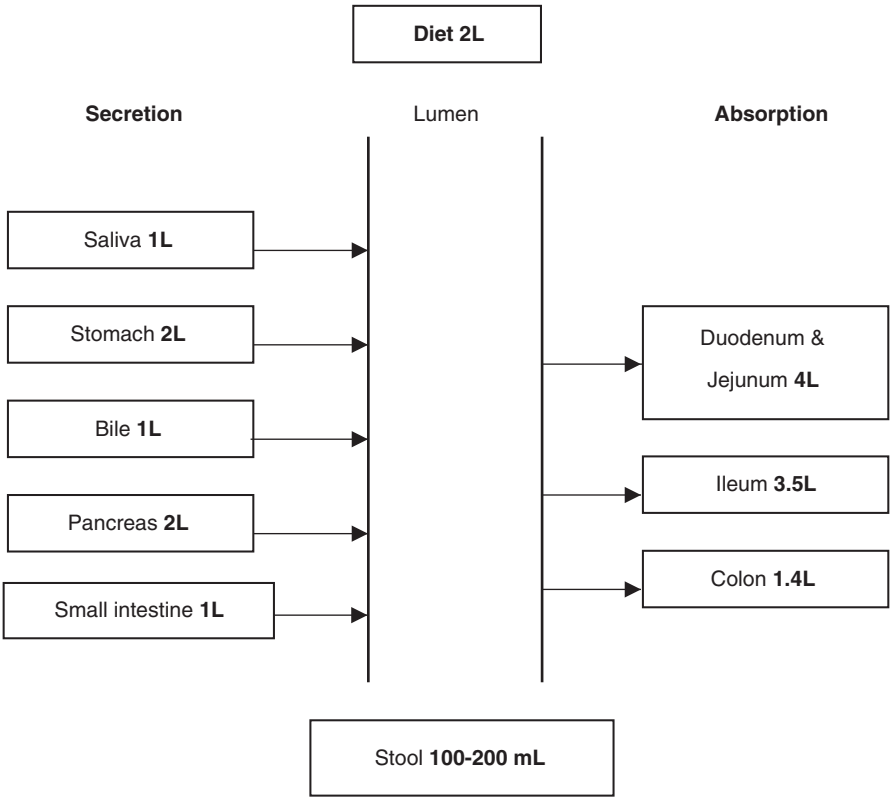

Fig. 9.1 Water handling by the normal gastrointestinal tract

- Thus, the daily total handling of water by the GI tract is 9 L.
- Of these 9 L, 4 L are absorbed by the duodenum and jejunum, 3.5 L by the ileum, and 1.4 L by the colon, leaving 100–200 mL in the stool.

Intestinal Electrolyte Transport

Na^+ and Cl^- Transport in the Small Intestine

- The epithelial cells lining the small intestine and colon absorb most of the delivered electrolytes and water in isoosmolar concentrations. Thus, the fluid that is absorbed is always *isosmotic*. The absorption of Na^+ and Cl^- in the small intestine is similar to that of the proximal tubule; however, a Cl/HCO_3 exchanger is localized which transports Cl^- into the cell in exchange for HCO_3^-. This chloride anion exchanger is also called downregulated in adenoma (DRA). Thus, NaCl

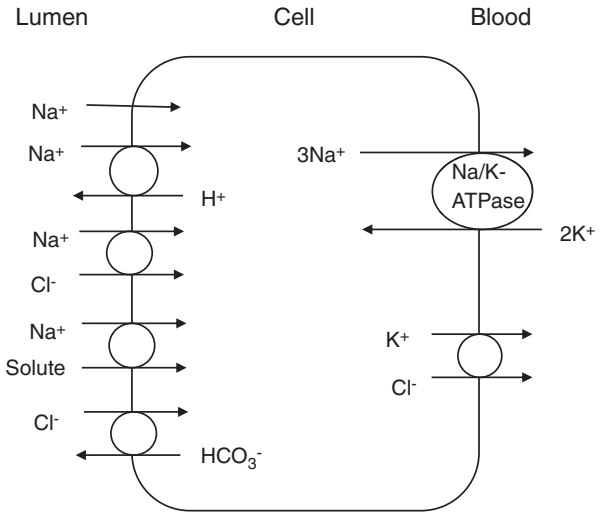

Fig. 9.2 NaCl transport in the epithelium of small intestine. Solute refers to glucose and amino acids

absorption occurs along the small intestine. The following transport mechanisms are responsible for NaCl entry into the cell (Fig. 9.2):

1. Na^+ transport alone via water channels
2. Na/H-ATPase with generation and absorption of HCO_3^-
3. Na/Cl cotransporter
4. Na^+ transport coupled with solutes (glucose, amino acids, etc.)
5. Cl/HCO_3 exchanger
6. Na^+ and Cl^- exit via Na/K-ATPase and K/Cl cotransporter, respectively

Na^+ and K^+ Transport in Colon

- The colon has both absorptive and secretory functions.
- Like principal cells, the epithelial cells of the colon contain Na^+ (epithelial Na^+ channel or ENaC) and K^+ channels separately (Fig. 9.3).
- Absorption of Na^+ and secretion of K^+ occur via their respective channels.
- Aldosterone regulates both Na^+ and K^+ transport.

Intestinal Secretion of Cl^-

- The epithelial cells lining the intestinal crypts secrete both electrolytes and water.
- The apical membrane of crypt cells contains Cl^- channels, and the basolateral membrane contains Na/K-ATPase, Na/K/2Cl cotransporter, and a K^+ channel. Na^+, K^+, and Cl^- enter the cells from blood via these transporters. Cl^- is secreted

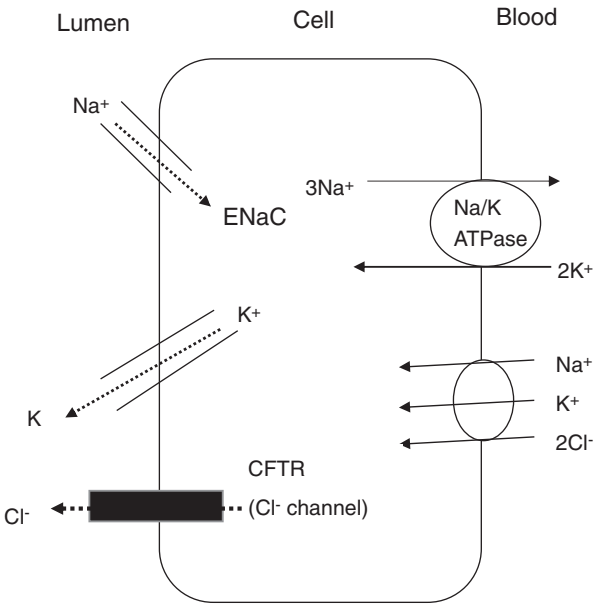

Fig. 9.3 Na^+ reabsorption and K^+ and Cl^- secretion in colon. ENaC epithelial sodium channel, CFTR cystic fibrosis transmembrane conductance regulator

into the lumen via Cl^- channel, whereas Na^+ enters the lumen passively via the paracellular pathway. Subsequently, water moves into the lumen following NaCl secretion.

- Usually, Cl^- channels are closed but remain open following activating substances. These substances bind to their receptor at the basolateral membrane, leading to the stimulation of adenylate cyclase and production of cAMP in crypt cells. cAMP then keeps Cl^- channel open, facilitating its secretion into the lumen.
- Cystic fibrosis transmembrane conductance regulator (CFTR) was identified as the Cl^- channel that is located in the apical membrane of epithelial cells. It mediates efflux of Cl^- into the lumen, thus involved in secretory function of the colon. CFTR is defective in cystic fibrosis, resulting in less Cl^- efflux (Fig. 9.3).

HCO_3^- Handling in the Colon

- Although HCO_3^- is secreted in the colon, all of it is not excreted in the stool. Most of this HCO_3^- is used up for the production of organic acids such as propionic acid, butyric acid, acetic acid, and lactic acid. These acids are the products of unabsorbed carbohydrates that are fermented by bacteria.
- Titration of these acids by $NaHCO_3$ generates sodium propionate, sodium butyrate, and other organic acids, which enter the liver for regeneration of HCO_3^-. Therefore, the stool contains low HCO_3^-.

Volume and Electrolyte Concentrations of GI Fluids

- Table 9.2 shows the normal values of electrolytes in various fluids of the GI tract. The information is useful in assessing the acid–base disturbances due to GI disorders.
- It is evident from Table 9.2 that the GI tract as a whole absorbs all the secreted Na^+ and Cl^-, leaving very few milliequivalents in the stool.
- More specifically, the jejunum absorbs about 100 mEq of Na^+ and 3 L of water, whereas the ileum absorbs 400 mEq each of Na^+ and Cl^- as well as 3.5 L of water.
- Finally, the colon is the most efficient segment of the intestine, absorbing >90% of 200 mEq of Na^+, 100 mEq of Cl^-, and 1.4 L of water delivered to it. Because of this tremendous absorptive capacity of the colon, the stool contains <100–200 mL of water and low quantities of Na^+, Cl^-, and HCO_3^-; however, K^+ concentration in stool is more than the other electrolytes because of its secretion in the colon.

Diarrhea

Water and Electrolyte Loss

- Diarrhea is defined when stool weight exceeds >200 g/day or >200 mL/day, when secretions of fluids exceed their absorption.
- Diarrhea is the most common nonrenal cause of hyperchloremic metabolic acidosis.
- Unlike renal acidoses where hyperchloremic metabolic acidosis is due to defects in transport mechanisms, diarrhea or GI disorders-induced hyperchloremic metabolic acidosis is due to loss of HCO_3^- and other electrolytes in the stool.
- The composition of the diarrheal fluid varies depending on the etiology of diarrhea (Table 9.3).

Table 9.2 Volume and concentrations of electrolytes in fluids of normal GI tract

Source	Volume (L/day)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)
Saliva (meal stimulated)	1	50–88	20	50	60
Gastric fluid (stimulated)	2	10–20	5–14	130–160	0
Bile	1	135–155	5–10	80–110	20
Pancreatic fluid	2	120–160	5–10	30–76	70–120
Small intestinal fluid	1	75–120	5–10	70–120	30
Stool	0.1–0.2	20–30	55–75	15–25	30

Table 9.3 Volume and electrolyte composition of diarrheal fluid

Etiology of diarrhea	Volume (L/day)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)
Stool (normal)	0.1–0.2	20–30	55–75	15–25	30
Osmotic	1–5	5–20	20–30	5–10	10
Secretory	1–20	75–140	15–40	75–105	30–75
Inflammatory (due to bowel disease) or infectious	1–3	50–100	15–20	50–100	10

Types of Diarrhea

- Diarrhea is usually classified into the following types:
  1. Osmotic diarrhea (due to laxatives, poorly absorbed carbohydrates such as lactulose) characterizes loss of more water than electrolytes
  2. Secretory diarrhea (increased secretions of water and electrolytes due to cholera, *Escherichia coli*-induced enterotoxin, or hormones such as vasointestinal polypeptide, or bile acids) causes more electrolyte than water loss
  3. Inflammatory diarrhea (due to loss of intestinal absorptive surface, cytokines)
  4. Infectious diarrhea (due to loss of intestinal absorptive surface, cytokines)
- Table 9.3 shows the diarrheal fluid volume and electrolyte composition in various types of diarrhea

  It is evident from Table 9.3 that diarrhea causes the following:

1. Na^+ loss and volume depletion: hypernatremia in osmotic diarrhea if no water intake and hyponatremia in secretory diarrhea with water intake
2. HCO_3^- loss in the stool: colonic HCO_3^- secretion is increased in secretory diarrhea; however, in other types of diarrhea, colonic loss may be offset by regeneration by the kidney. Persistent stool losses as well as inability of the kidney to secrete H^+ in the urine due to severe volume depletion can cause acidosis
3. K^+ loss in the stool: hypokalemia occurs due to stool and renal loss mediated by aldosterone. Also, less K^+ intake may contribute to hypokalemia

Diagnosis

- History, physical examination, and medications are important.
- Serum electrolytes, Ca^{2+}, Mg^{2+}, phosphate, albumin, and arterial blood gas (ABG).

- Urine anion gap (U_{AG}) is helpful in distinguishing between renal and nonrenal acidoses. U_{AG} is negative in diarrhea and positive in renal acidoses.
- Urine pH is <5.5 in moderate diarrhea and >6.5 in severe diarrhea because of volume depletion and increased urinary excretion of NH_4^+.
- Stool osmolal gap is not routinely calculated but is helpful in diagnosing the type of diarrhea.

Method of Calculating Stool Osmolal Gap

- Centrifuge at least 1.5 g of fresh stool and separate supernatant from precipitate.
- Measure osmolality and electrolytes in supernatant.
- Calculate osmolal gap (mOsm/kg) as follows:
- Osmolal gap (mOsm/kg) = measured osmolality $-2 \times (Na^+ + K^+)$, where 2 accounts for the unmeasured anions accompanying the measured cations

Interpretation

A positive value ≥50 mOsm/kg indicates unmeasured osmoles suggestive of osmotic diarrhea.

A negative value or a smaller positive value indicates secretory diarrhea.

Types of Acid–Base Disorders in Diarrhea

- In mild to moderate diarrhea, only hyperchloremic metabolic acidosis occurs (a decrease in serum [HCO_3^-] is accompanied by a proportionate increase in serum [Cl^-]), resulting in normal AG.
- However, mixed acid–base disorders are commonly seen in diarrheal states in the following clinical situations:

1. Uncomplicated diarrhea: hyperchloremic metabolic acidosis (HCMA)
2. Diarrhea + hypovolemia + hypotension or sepsis: HCMA + lactic acidosis
3. Diarrhea + vomiting: HCMA + metabolic alkalosis
4. Diarrhea + hyperventilation (gram-negative enteric pathogen): HCMA + respiratory alkalosis
5. Diarrhea + sepsis + pneumonia: HCMA + lactic acidosis + respiratory alkalosis

Figure 9.4 illustrates the pathogenesis of HCMA and other acid–base disorders in diarrhea

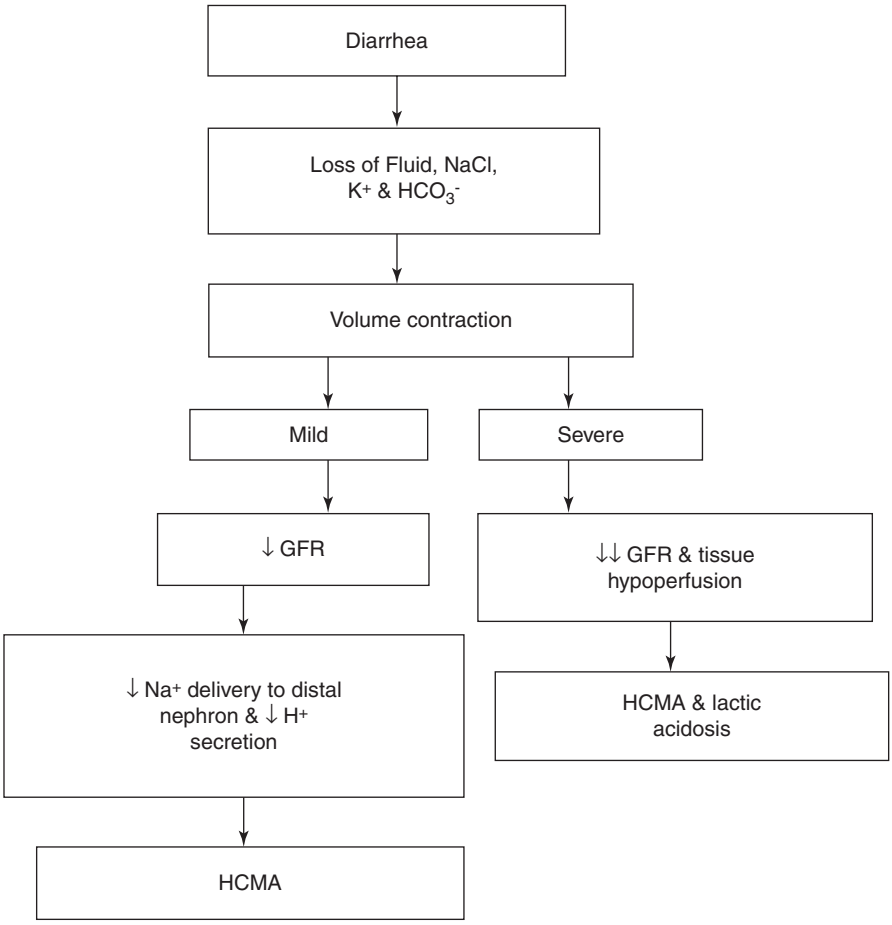

Fig. 9.4 Pathogenesis of hyperchloremic metabolic acidosis (HCMA) and combined lactic acidosis and HCMA in diarrhea. *GFR* glomerular filtration rate

Treatment

- Normal saline is required to replace volume loss, if there is mild volume depletion.
- Correction of volume deficit is crucial to improve renal function and facilitate H^+ secretion for regeneration of HCO_3^- by the kidney.
- Provide 0.45% saline with 75 mEq of $NaHCO_3$ to improve serum [HCO_3^-] for severe acidemia. Treat hypokalemia with KCl prior to $NaHCO_3$ infusion, as $NaHCO_3$ lowers serum [K^+] even further. Ringer's lactate can be used in selected patients following volume replacement.
- Treat the underlying cause of diarrhea simultaneously with replacement of fluid and electrolytes.

- In patients with acute or chronic noncholera diarrhea, oral replacement solution may be required. The standard World Health Organization Oral Rehydration Solution (311 mOsm/L) contains Na^+ (90 mEq/L), Cl^- (80 mEq/L), K^+ (20 mEq/L), glucose (111 mmol/L), and citrate (10 mEq/L). Some studies have shown that low osmolality solutions are associated with reduction in stool volume and duration of diarrhea.
- Targeting ion transporters is another way to treat secretory and inflammatory diarrhea. Inhibition of CFTR channel may decrease excess Cl^- secretion. Stimulation of Na/H exchanger and/or Cl/HCO_3 activity or their abundance may increase the production of HCO_3^- and Cl^- reabsorption, respectively. Many bacteria that cause diarrhea alter several transport mechanisms that warrant further research for the production of antidiarrheal agents.

Biliary and Pancreatic Fistulas

- Recall that bile and pancreatic secretions amount to 3 L and the $[HCO_3^-]$ is approximately 200–300 mEq.
- Consequently, any enterocutaneous fistulas or catheters draining any of these secretions can generate HCMA by losing HCO_3^- in excess of Cl^-.

Villous Adenoma

- Usually found in the colon with capacity to undergo malignant transformation.
- Interestingly, both HCMA due to loss of HCO_3^- in the stool and metabolic alkalosis due to loss of Cl^- have been described.
- Prevention of severe volume depletion and resection of the tumor improve the acid–base disorder.

Urinary-Intestinal Diversions

- When the ureter or bladder is damaged, a diversion for urine to pass through a segment of the GI tract is created.
- The urine that enters the GI tract facilitates Cl^- absorption and HCO_3^- secretion via the Cl/HCO_3 exchanger present in the colon. This exchange is accentuated when the urine remains for a long period of time in the bowl.
- Loss of HCO_3^- in the stool and accumulation of Cl^- in blood result in HCMA.
- HCMA is common in ureterosigmoidostomy and less common with ureteroileostomy, because of rapid drainage of urine into ileostomy bag.

- Another way of HCMA development is absorption of NH_4^+ derived from urine and urea by the colon. Absorbed NH_4^+ is converted to NH_3 and H^+, and NH_3 is subsequently converted into urea. When a disturbance of this conversion occurs, acidosis develops.
- Note that patients with ureteral diversions may have other causes such as obstructive uropathy for HCMA.
- Hypokalemia results from active Na^+ absorption with creation of a favorable voltage gradient for K^+ secretion and also from secondary hyperaldosteronism.
- Treatment of HCMA depends on the severity of acidosis and volume status.

Laxative Abuse

- Laxative abuse is rather common mostly in younger women.
- Mild to moderate hypokalemic HCMA develops.
- Some patients may also develop metabolic alkalosis.
- Diagnosis is usually suspected when patients complain of alternating constipation and diarrhea, HCMA, and hypokalemia.
- The above clinical manifestations and hypermagnesemia suggest the use of Mg^{2+}-containing laxatives. Urine pH is >7 in these subjects.
- Phenolphthalein-containing laxatives stain pink with either NaOH or KOH.
- Treatment is correction of volume depletion and stopping laxative abuse by education as well as addressing psychiatric issues, if any.

Cholestyramine

- As an anion-exchange resin, cholestyramine is used to treat hypercholesterolemia. It also binds bile acids.
- As a resin, it adsorbs HCO_3^- and releases Cl^-, which is subsequently reabsorbed, resulting in HCMA.

Study Questions

Case 1 An 18-year-old female student is admitted for weakness, tiredness, and loose stools for 1 week. She denies diarrhea or any type of medications but admits to frequent urination. Physical examination reveals that she is thin with no apparent distress. Blood pressure is 100/60 mmHg with a pulse rate of 94 beats per minute with orthostatic changes. She is afebrile. Lungs and heart are normal. Abdomen is soft with no tenderness. There is no peripheral edema. Laboratory results:

Serum	Urine
Na^+ = 132 mEq/L	pH = 6.4
K^+ = 2.8 mEq/L	Osmolality = 800 mOsm/kg H_2O
Cl^- = 115 mEq/L	Na^+ = 20 mEq/L
HCO_3^- = 15 mEq/L	K^+ = 15 mEq/L
Creatinine = 1.5 mg/dL	Cl^- = 55 mEq/L
BUN = 30 mg/dL	
Glucose = 90 mg/dL	
Albumin = 4.2 g/dL	
ABG: pH = 7.32; PCO_2 = 30 mmHg; PO_2 = 98 mmHg; HCO_3^- = 14 mEq/L	

BUN blood urea nitrogen, *ABG* arterial blood gas

Question 1 What is the acid–base disturbance in this patient?

Answer HCMA with appropriate respiratory response.

Question 2 Which one of the following best describes the observed abnormalities in serum chemistry?

A. Distal renal tubular acidosis (RTA)
B. Diuretic abuse
C. Laxative abuse
D. Proximal RTA
E. Surreptitious vomiting

The answer is C. On the basis of the urine pH and HCMA, distal RTA can be considered; however, urine electrolytes do not support this diagnosis. Diuretic abuse may cause volume depletion and orthostatic changes, but urine pH, osmolality, and electrolyte pattern do not support diuretic abuse. Also, diuretics such as furosemide and hydrochlorothiazide cause metabolic alkalosis rather than metabolic acidosis. Carbonic anhydrase inhibitors such as acetazolamide cause HCMA with alkaline urine pH and proximal RTA; however, urine lytes do not support acetazolamide abuse. Proximal RTA is also unlikely because the urine pH is usually <5.5 with serum [HCO_3^-] of 15 mEq/L. Urine pH and electrolytes do not suggest late vomiting, as early and late vomiting cause low Cl^- and high K^+ excretion. During early vomiting, the urine pH is alkaline because of HCO_3^- excretion, and during late vomiting, pH is acidic because of H^+ secretion. Thus, options A, B, D, and E are incorrect.

The patient agrees to laxative abuse, which is confirmed by stool testing with NaOH. Laxative abusers will have diarrhea-induced volume depletion and the electrolyte abnormalities as described earlier.

Question 3 Why is her urine pH alkaline rather than acidic as in diarrhea?

Answer Generally, diarrhea causes acidic urine pH. However, when volume depletion is severe owing to diarrhea, NH_4^+ excretion is increased, which raises urine pH.

Question 4 Is there any evidence in this patient that NH_4^+ excretion increased?

Answer Yes. The U_{AG} is negative ($U_{Na} + U_K - U_{Cl}$ or 20 + 15–55 = − 20), suggesting high NH_4^+ excretion. This test also rules out both proximal and distal RTAs.

Case 2 A 55-year-old man with HIV is admitted for profuse diarrhea, volume depletion, and weakness. Despite highly active antiretroviral therapy (HAART) medications, diarrhea developed 10 days ago with gradual worsening of his symptoms. Blood pressure, electrolytes, and ABG are similar to case 1, except for blood pH of 7.20.

Question 1 How would you manage this patient?

Answer There are three major diarrhea-induced complications in this patient: (1) volume depletion; (2) hypokalemia; and (3) severe metabolic acidosis.

Volume Depletion and Hypokalemia Normal saline is the fluid of choice, as he has orthostatic blood pressure and pulse changes. Hypokalemia should be corrected before infusion of normal saline, as volume expansion improves glomerular filtration rate (GFR) and promotes K^+ excretion. Oral KCl is always preferred to i.v. KCl if the patient can take it by mouth. Otherwise, i.v. KCl 20 mEq/L/h can be given. Another way (some physicians prefer) is adding 75 mEq of KCl to 0.45% saline to make the fluid isotonic. Infusion of 200–250 mL/h for 4 h will improve volume and blood pressure status. This regimen should be continued with less infusion of fluid until serum [K^+] is >3.5 mEq/L, and then assess the need for KCl supplementation.

Some physicians prefer Ringer's lactate to replenish electrolytes, but volume expansion and correction of Na^+ is less than normal saline. Intravenous K-citrate can also be given once renal function is normalized.

Correction of Acidosis Once hypokalemia and volume are partially corrected, serum [HCO_3^-] decreases. Therefore, $NaHCO_3$ should be given to improve [HCO_3^-] and pH. One needs to calculate ΔHCO_3^-, and then $NaHCO_3$ should be given, as shown in the following example:

$$\text{Body weight} = 70\,\text{kg}$$
$$HCO_3^- \text{space} = 50\%$$
$$\Delta HCO_3^- = 4\left(\text{increase from } 15 \text{ to } 19 \text{ mEq}\right)$$
$$\text{Required } NaHCO_3 \text{ to raise serum } HCO_3^- \text{ from } 15 \text{ to } 19\,\text{mEq/L}:$$
$$70 \times 0.5 \times 4 = 140\,\text{mEq}$$

Add 140–150 mEq of $NaHCO_3$ to 5% dextrose in water (D5W) and infuse over 6–8 h; provided serum [K^+] is >3.5 mEq/L; otherwise, hypokalemia develops.

The cause of diarrhea should be investigated and treated appropriately. Osmotic diarrhea will improve with fasting, but not secretory diarrhea.

Question 1 *Match the following electrolyte and ABG values with the case histories:*

A. Patient with simple diarrhea
B. Patient with diarrhea and vomiting
C. Patient with diarrhea and lactic acidosis
D. Patient with diarrhea and respiratory alkalosis due to pneumonia

Option	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	pH	pCO_2 (mmHg)
1	138	2.4	120	9	7.32	18
2	140	3.2	116	5	7.13	14
3	134	2.8	104	23	7.40	38
4	136	3.1	114	12	7.28	26

Answers *A = 4*; *B = 3*; *C = 2*; *D = 1*. Calculation of serum AG is helpful, because lactic acidosis is associated with elevated AG. The serum AG in option 2 is 19, and therefore associated with case C. All other cases have normal serum AG.

Patient with diarrhea and vomiting should have near-normal serum [HCO_3^-] compared with other cases, because vomiting is associated with low serum [Cl^-]. Serum pH should be normal (diarrhea causes low pH and vomiting raises pH. When both coexist, the pH becomes normal). Thus, option 3 corresponds to case B.

Patient with diarrhea and respiratory alkalosis should have relatively low HCO_3^-, high Cl^-, and near-normal pH. Electrolytes and ABG described in option 1 are consistent with case D.

Uncomplicated diarrhea is associated with moderate acidemia, and electrolyte and ABG pattern are consistent with option 4.

Suggested Reading

Atia AN, Buchman AL. Oral rehydration solutions in non-cholera diarrhea: a review. Am J Gastroenterol. 2009;104:2596–604.

Batlle DC. Hyperchloremic metabolic acidosis. In: Seldin DW, Giebisch G, editors. The regulation of acid-base balance. New York: Raven Press; 1989. p. 319–51.

Camilleri M, Sellin JH, Barrett KE. Pathophysiology, evaluation, and management of chronic watery diarrhea. Gastroenterology. 2017;152:515–32.

Charney AN, Danowitz M. Gastrointestinal influences on hydrogen ion balance. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 209–40.

Das S, Jayaratne R, Barrett KE. The role of ion transporters in the pathophysiology of infectious diarrhea. Cell Mol Gastroenterol Hepatol. 2018;6:33–45.

Field M. Intestinal ion transport and the pathophysiology of diarrhea. J Clin Invest. 2003;111:931–43.

Gennari FJ, Weise WJ. Acid-base disturbances in gastrointestinal disease. Clin J Am Soc Nephrol. 2008;3:1861–8.

Ghishan FK, Kiela PR. Small intestinal ion transport. Curr Opin Gastroenterol. 2012;28:130–4.

Kent AJ, Banks MR. Pharmacological management of diarrhea. Gastroenterol Clin North Am. 2010;39:495–507.

Kraut JA, Kurtz I. Treatment of non-anion gap metabolic acidosis. Clin Kidney J. 2015;8:93–9.

Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: mechanisms and implications for disease. Physiol Rev. 2002;82:245–89.

Wesson DE, Laski M. Hyperchloremic metabolic acidosis due to intestinal losses and other non-renal causes. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 487–99.

Chapter 10
Acid–Base Disorders in Kidney Disease

This chapter reviews acid–base disorders in acute kidney injury (AKI), chronic kidney disease (CKD), hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. Most of these conditions are associated with high anion gap (AG) acidosis. Depending on the etiology of AKI, however, other acid–base disorders such as hyperchloremic (non-AG) acidosis, metabolic alkalosis, respiratory alkalosis, or respiratory acidosis may coexist with AG metabolic acidosis. The coexistence of lactic acidosis, ketoacidosis, and toxin ingestion in AKI patients may increase AG even further. Thus, mixed acid–base disorders are not uncommon in patients with kidney disease.

Acute Kidney Injury (AKI)

As discussed in Chap. 2, a normal subject generates 1 mEq/L/kg of fixed acid which has to be excreted. In AKI, this acid excretion is impaired. Therefore, metabolic acidosis develops with high AG. This is the most common acid–base disorder in AKI. Other acid–base disorders that complicate AKI are shown in Table 10.1.

Treating etiology of metabolic and respiratory acid–base disorders is an important aspect in the management of AKI. Use of $NaHCO_3$ and at times renal replacement therapies improve not only acidosis but renal function as well.

Chronic Kidney Disease (CKD)

As stated in AKI, acid–base balance is disturbed when daily acid production is not excreted. Elimination of acid load is achieved by appropriate excretion of titratable acid and NH_4^+ (net acid excretion; see Chap. 2). With development of CKD, the number of functioning nephrons decreases, and the patients retain acid load because

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_10

Table 10.1 Acid–base disorders in AKI

Acid–base disorder	Mechanism	Comment
High AG metabolic acid	Accumulation of endogenous acids such as sulfate and phosphates	Most common disorder
Very high AG metabolic acidosis	Accumulations of lactic acid (sepsis, hypoxia, etc.), ketoacids, and toxins	Rather common in critically ill patients
High AG and non-AG metabolic acid	Accumulation of sulfates and phosphates with HCO_3^- loss due to diarrhea or renal tubular acidosis. $\triangle AG/\triangle HCO_3^- < 1$ is usually seen in patients with diarrhea	Infrequent acid–base disorder
High AG metabolic acidosis and metabolic alkalosis	Removal of acid with vomiting and nasogastric suction in the presence of sulfates and phosphates. Patients receiving blood transfusions with citrated blood	Rather common in AKI patients following intubation
High AG metabolic acidosis and respiratory alkalosis	Patient with AKI and pneumonia, sepsis, or central nervous system infections	Rather common acid–base disorder
High AG metabolic acidosis and respiratory acidosis	AKI in patients with COPD or other conditions of CO_2 retention	Uncommon acid–base disorder in AKI
Low AG metabolic acidosis	AKI due to IgG myeloma	Infrequent acid–base disorder

of decreased NH_4^+ excretion. Most of the studies analyzed acid–base status in CKD based on serum bicarbonate concentration ($[HCO_3^-]$) measured by an autoanalyzer or by ABG machine as calculated $[HCO_3^-]$. Based on these measurements, the prevalence of metabolic acidosis, which is the major acid–base disturbance in CKD, has been estimated at different stages of CKD. Acidosis or low bicarbonate was usually defined as serum $[HCO_3^-]$ <22 mEq/L. A few studies document the prevalence of acidosis in predialysis CKD patients, as reviewed by Abramowitz [1] and Chen and Abramovitz [2]. According to the Nephro Test Cohort Study from France [2], the overall prevalence of metabolic acidosis in patients with CKD stages 1–4 was found to be 8%, and the severity of acidosis increases with decreases in eGFR (i.e., progression of kidney disease). In the Chronic Renal Insufficiency Cohort (CRIC) study, the prevalence of low $[HCO_3^-]$ (<22 mEq/L) in patients with eGFR 20–70 mL/min was 17.3% [2], and the decline in $[HCO_3^-]$ increased with decline in eGFR (7% in CKD 2, 13% in CKD 3, and 37% in CKD 4) [2]. In the African American Study of Kidney Disease and Hypertension (AASK) study, the measured GFR in participants was between 20 and 65 mL/min. Their mean serum $[HCO_3^-]$ was 25.1 mEq/L; however, the distribution was <20 mEq/L in 4.3%, 20–24.9 mEq/L in 35.5%, and ≥30 mEq/L in 5.5% of participants. Similar to other studies, serum $[HCO_3^-]$ decreased with lower GFR levels. These three important studies suggest that metabolic acidosis is associated with decreased kidney function [2]. It should be noted that serum $[HCO_3^-]$ does not fall <16 mEq/L in most of the CKD patients because of buffering of the acid load by bone. However, there are several factors that may lower serum $[HCO_3^-]$, including high protein intake, albuminuria, smoking, and converting enzyme inhibitors. Both the decrease in HCO_3^- and increase in AG were found to be associated with all-cause mortality and morbidity.

Net Acid Excretion in CKD (NAE)

NAE represents the amount of urinary buffers that are responsible for the excretion of H^+ in the urine. These urinary buffers are titratable acidity (TA) in the form of $H_2PO_4^-$ and NH_4^+ (see Chap. 2). Acidosis enhances NAE to maintain normal acid–base balance. In CKD, the functioning mass decreases; however, the remaining nephrons get hypertrophied and increase their GFR.

The rate of TA excretion depends on phosphate filtration and its excretion. In CKD, filtration of phosphate increases, but its reabsorption in the proximal tubule is decreased. This reduced phosphate reabsorption is due to an increase in fibroblast growth factor-23 and parathyroid hormone. As a result, more phosphate is delivered to the distal tubule, and the formation of TA is slightly increased or normal. Thus, the rate of TA in CKD is maintained usually at normal levels.

In comparison to TA, the excretion of NH_4^+ is decreased. In CKD, the functioning hypertrophied nephrons generate and excrete more NH_4^+. When acid load increases, the excretion of NH_4^+ is decreased, and H^+ is retained with development of metabolic acidosis. This suggests that NH_4^+ is the major urinary buffer in normal individuals and CKD patients.

Thus, TA is preserved or slightly elevated, but NH_4^+ excretion decreases in CKD. Despite these changes, the urine pH remains <5.5. Although this is an acidic pH, it is slightly high when compared to that of a normal individual at comparable serum HCO_3^-level.

Pattern of Acid–Base Disorders

In early stages of CKD, a non-AG (hyperchloremic) metabolic acidosis develops because of impaired HCO_3^- reabsorption and its excretion, as shown by early studies. This is followed by the development of a mixed non-AG and high AG metabolic acidosis in some patients. With progression to nondialysis-dependent CKD 5, a high AG metabolic acidosis develops in the majority of the patients. Thus, CKD patients go through these two types of acid–base disorders prior to renal replacement therapies.

Some patients with hyporeninemic hypoaldosteronism may develop non-AG metabolic acidosis at higher GFRs. These patients have hyperkalemia that is disproportionate to their GFR, and their acidosis is more severe than other patients with similar GFRs. Hyperkalemia inhibits NH_3 genesis, causing decreased NH_4^+ formation.

Pathophysiology of Metabolic Acidosis

There are several mechanisms that are involved in the development of both non-AG and high AG metabolic acidosis in CKD. The major mechanism is a decrease in NH_4^+ excretion. These are presented in Table 10.2.

Table 10.2 Mechanisms of metabolic acidosis in CKD

1. Decreased NH_4^+ excretion and production by the failing kidney (GFR <15 mL/min) with positive H^+ balance
2. Decreased synthesis of NH_3 (NH_4^+) by hyperkalemia
3. Decreased conservation of HCO_3^- by the failing kidney
4. Insufficient titratable acid (phosphate) excretion compared to acid load
5. Increased production of anions (sulfate, phosphate) due to high protein intake
6. Increased catabolism in some malnourished patients generating sulfate and phosphate
7. Relative hypoaldosteronism due to diabetes, hypertension, interstitial disease, or drugs, such as ACE-Is, angiotensin receptor blockers, K^+-sparing diuretics, and NSAIDs, may aggravate metabolic acidosis by lowering GFR even further

Adverse Effects of Metabolic Acidosis

In general, chronic metabolic acidosis has several adverse effects irrespective of its etiology. In CKD, however, uremic toxins may aggravate these adverse effects. For detailed discussion of adverse effects of metabolic acidosis, the reader is referred to Wesson [3]. Table 10.3 shows the most commonly observed effects of metabolic acidosis:

Treatment

The 2013 KDIGO guidelines (see Suggested Reading) make the following statement regarding treatment of metabolic acidosis as "We suggest that in people with bicarbonate concentration <22 mmol/L treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated (2B)."

Based on the above recommendation, it is important to normalize serum [HCO_3^-] in patients with mild to severe metabolic acidosis using bicarbonate, particularly $NaHCO_3$. Sodium citrate can be substituted in case of intolerance to $NaHCO_3$ therapy. There are two important ways to increase serum [HCO_3^-] using base therapy. These include (1) use of $NaHCO_3$ or sodium citrate and (2) to reduce dietary acid load.

Use of $NaHCO_3$ or Sodium Citrate

Table 8.3 (see Chap. 8) shows various forms of alkalizing agents available for treatment of low serum [HCO_3^-]. K-containing bases should be avoided in patients with CKD because of hyperkalemia. Sodium citrate is more expensive than $NaHCO_3$.

Table 10.3 Adverse effects of metabolic acidosis

Adverse effect	Mechanism
Muscle wasting	Due to muscle protein degradation mediated by upregulation of ubiquitin-proteasome pathway and caspase-3 protease. Acidosis activates glucocorticoid effect on protein degradation. However, total protein synthesis is not affected. Administration of base improves lean body mass
Hypoalbuminemia	Chronic acidosis was found to decrease albumin synthesis as opposed to muscle total protein synthesis. Hypoalbuminemia has been reported in CKD patients with low GFR and HCO_3^- levels. Administration of base to CKD patients improves albumin levels
Progression of kidney disease	Several studies have shown progression of kidney disease in patients with lower serum HCO_3^- levels. Potential mechanisms include an increase in AII, aldosterone, and endothelin levels, which promote renal fibrosis. Increased NH_4^+ genesis by the surviving nephrons activates complement and inflammation with resultant fibrosis. Chronic acidosis may activate growth factors, cytokines, and chemokines that promote renal fibrosis. It should be noted that renal tubular acidosis may not be associated with progression of kidney disease
Bone disease	Not only abnormal vitamin D metabolism but also chronic acidosis cause bone disease in CKD. Kidney disease alone increases PTH and decreases calcitriol levels. Both cause release of Ca^{2+} salts from bone with resultant development of osteomalacia and renal osteodystrophy. Acidosis also stimulates PTH secretion. Bone buffers H^+ in CKD with resultant decrease in bone minerals. Thus, chronic metabolic acidosis contributes to bone disease
Insulin resistance	Insulin action is decreased in metabolic acidosis because of decreased insulin binding to its receptor. Thus, glucose intolerance is common in CKD
Growth hormone, IGF-1, and thyroid hormones	Chronic acidosis lowers levels of these hormones in CKD. Blunted IGF-1 response to growth hormone has been reported
Increased inflammation	Acidosis stimulates the release of pro-inflammatory cytokines from macrophages
Cardiac contractility	Severe acidosis impairs cardiac contractility via less Ca^{2+} binding to troponin and disturbed interaction between actin and myosin

The recommended dose of $NaHCO_3$ is 0.5 to 1 mEq/kg/day in divided doses until serum [HCO_3^-] is normal and then continue maintenance dose. Each 650 mg tablet of $NaHCO_3$ contains 8 mEq of bicarbonate. Probably these tablets bought from any pharmacy are better than taking baking soda from supermarkets.

$NaHCO_3$ has some untoward effects such as production of CO_2 gas in GI tract and Na-overload in patients with heart failure. However, data from one study showed that daily intake of 200 mEq (17 g) of $NaHCO_3$ did not cause any fluid retention when compared with NaCl ingestion. Metabolic alkalosis is another complication of bicarbonate therapy. Frequent physical examination and evaluation of serum chemistry is required in the management of chronic metabolic acidosis.

Reduction of Dietary Acid Load

A typical American diet generates approximately 1 mEq/kg/day of fixed acid. This is mostly due to animal-derived protein intake. A patient with severe metabolic acidosis generates 1 mEq/kg/day of acid from high protein diet, and the renal prognosis of this patient is poor. Thus, daily acid load should be decreased in such a patient by recommending foods that generate low H^+ production (acid load). Measurement of NAE is an index of acid load. Remer and associates (reference cited in Table 10.4) developed a model for this acid load called potential renal acid load (PRAL), which is helpful in preparing daily required food. Table 10.4 shows PRAL for different foods.

From Table 10.4, one can understand that foods with PRAL less than zero are considered to have an alkaline effect in the body, and foods that have a higher value than zero will have an acidifying effect in the body. For example, diet that contains more vegetables and fruits will increase serum [HCO_3^-], whereas diet that is rich in protein will lower serum [HCO_3^-], particularly in CKD patients. Thus, animal-derived foods contribute more acid load than vegetable- and fruit-derived foods.

Table 10.4 Daily acid load of certain foods

Type of food	Acid load (PRAL) (mEq/100 g edible food)
Fats and oils	0
Vegetables	−2.8
Fruits and fruit juices	−3.1
Potatoes	−4.0
Bread	3.5
Flour	7.0
Fish	7.9
Meat and meat products	9.5
Turkey	9.9
Milk with noncheese products	1.0
Cheese with lower protein content	8.0
Cheese with higher protein content	23.6
Parmesan cheese	34.2
Brown rice	12.5
White rice	4.6
White flour bread	1.8
Red wine	−2.4
Strawberry	−2.2
Hazelnet	−2.8
Carrots	−4.9

Adapted from Remer T, *Sem Dial* 2000;13:221–36, and Angélico LRN, et al. *J Renal Nutr* 2018;28:215–20

Table 10.5 Example of a diet with low acid load

Food	Protein content (/100 g)	Acid load (mEq/100 g)
White rice	7.3	4.6
Potatoes	2.1	−4
White flour bread	6.2	1.8
Textured soy protein meatball with tomato juice	20	−7.3
Egg white omelet	9	1.1
Low-fat cheese	13.8	1.2
Fresh beef	20.3	7.8
Red wine (100 mL)	0.2	−2.4
Strawberry	0.8	−2.2
Hazelnut	14.1	−2.8
Net acid excretion (NAE)		−1.93

Adapted from Angélico LRN, et al. *J Renal Nutr* 2018;28:215–20

Because of these alkaline properties of vegetables and fruits, they are better choices than the use of $NaHCO_3$ alone in CKD patients with metabolic acidosis.

Indeed, a well-designed study has suggested that ad libitum intake of base-generating fruits (oranges, apples, apricots, peaches, pears, strawberries, raisins) and vegetables (potatoes, tomatoes, carrots, cauliflower, eggplant, lettuce, spinach) to CKD 4 patients raised serum [HCO_3^-] and improved metabolic acidosis after 1 year of treatment. Also, markers of kidney injury were lower after fruit and vegetable diet. Serum [K^+] was not increased. Thus, fruit and vegetable diet improves metabolic acidosis and reduces kidney damage in CKD 4 patients without inducing hyperkalemia. One should be cautious in prescribing fruits and vegetables to CKD patients who have low GFRs and those prone to develop hyperkalemia such as diabetics to avoid hyperkalemia, as the above study excluded such patients.

Based on acid load of various foods, Angélico et al. (reference citation in Table 10.5) developed a diet that seems to be helpful in CKD patients with metabolic acidosis because of low acid load. Table 10.5 shows the composition of such a diet.

Since the above diet generates a negative NAE, the diet has an alkaline effect on body fluids, which is beneficial to a CKD patient with metabolic acidosis. This type of diet can be individualized for compliance without compromise in daily calories.

Hemodialysis (HD)

As discussed previously, most of the patients with CKD 5 develop severe metabolic acidosis with high AG. The major mechanisms for acidosis in dialysis-dependent patients include (1) decreased excretion of generated H^+ because of reduced renal function; (2) hypercatabolism; and (3) noncompliance to dietary and base

prescription. In chronic dialysis patients, predialysis serum HCO_3^- level should be maintained >22 mEq/L and midweek level around 27 mEq/L, as serum HCO_3^- levels <18 mEq/L and >27 mEq/L are associated with high morbidity and mortality. One of the major goals of HD is correction of acid–base balance.

Modern dialysate solutions contain HCO_3^- and its precursor acetate. Some dialysates contain citrate (citric acid) in place of acetate in the acid concentrate. The concentration of HCO_3^- in the dialysate varies from 35 to 37 mEq/L with acetate (acetic acid) from 4 to 8 mEq/L. Early studies showed that dialysate HCO_3^- levels >40 mEq/L may be necessary to correct acidosis in many patients. Transmembrane diffusion of HCO_3^- occurs between dialysate and blood. Once serum HCO_3^- level reaches to a certain higher level, transmembrane gradient of HCO_3^- is reduced, and its diffusion from dialysate to blood is also reduced. Diffusion of HCO_3^- resumes once its serum levels fall due to its conversion into CO_2 and its loss into water during ultrafiltration. Correction of acidosis depends not only on dialysate HCO_3^- level but also on interdialytic weight gain. For example, patients who gain significant amount of weight between dialysis treatments may require high dialysate HCO_3^- level to correct their acidosis, as compared with those who gain less weight. After dialysis treatment, the acetate is metabolized to HCO_3^-, and the patients may develop metabolic alkalosis. Because of protein intake of 1 g/kg/day or higher, metabolic alkalosis improves with acid load, and predialysis HCO_3^- level will be between 22 and 25 mEq/L in most of the patients. This is evident from routine blood work done each month in HD patients. However, some patients may have persistently higher HCO_3^- levels, and these patients require evaluation of their diet, volume status, medications, and adjustment of their dialysate HCO_3^- concentration.

Individualizing dialysate HCO_3^- concentration is an important concept to prevent predialysis acidosis (i.e., <22 mEq/L) and postdialysis alkalosis. Although individualization is not feasible in all patients, it is important to maintain near-normal serum HCO_3^- level in patients with bone disease to prevent bone dissolution. Some of the patients may benefit from the use of citrate than acetate in the dialysate acid concentrate. Citrate is not only metabolized to HCO_3^-, but it has local anticoagulant effect on the dialyzer membrane as well. As a result, the membrane permeability to HCO_3^- is increased.

It should be noted that rapid correction of acidosis in a new patient has some adverse effects such as altered mental status, hypokalemia, cramps, and cardiac arrhythmias. Therefore, gradual correction of acidosis is required. Hypoxemia is another complication of HCO_3^- use. Sudden increase in serum HCO_3^- level may raise pH with resultant suppression of ventilation.

Metabolic alkalosis occurs following completion of dialysis treatment. As stated above, this is related to transfer of HCO_3^- from dialysate to blood. In addition, other factors such as blood transfusion due to citrate, regional anticoagulation with citrate, and extensive use of crack cocaine may cause metabolic alkalosis. Crack cocaine may contain base as a contaminant. Nausea and vomiting are rare causes of metabolic alkalosis in a chronic HD patient. Mixed acid–base disorders are rather uncommon unless the patient has predisposition to respiratory acidosis or alkalosis.

Peritoneal Dialysis (PD)

The current PD solution contains lactate (35 or 40 mM) as the buffer, which is used universally. After discontinuation of acetate as a buffer, lactate was introduced. Lactate is an intermediate of citric acid cycle and is metabolized to HCO_3^- in the liver. A third solution consisting of lactate and HCO_3^- was introduced, which is pH neutral but not that popular as lactate-containing dialysate. Another PD solution that contains only HCO_3^- (34 mM) was introduced as a two-bag system by Fresenius Medical Care. During routine PD treatment, lactate diffuses into the blood, and HCO_3^- enters the dialysate. This diffusion is rapid during the first hour and gradually slows down in the remaining time.

In HD, the predialysis HCO_3^- is low and postdialysis is high. This up and down HCO_3^- levels are not seen in PD patients because the lactate is constantly converted into HCO_3^- and improves metabolic acidosis. Acid–base balance is achieved during both continuous ambulatory PD and automated PD.

Metabolic alkalosis was infrequently reported in PD patients. If it occurs, it was attributed to low-protein intake causing low acid load. Lactic acidosis has been reported in patients with liver disease who cannot metabolize lactate to HCO_3^-, but it is a rare adverse effect.

Kidney Transplantation

The discussion of metabolic acidosis has largely been neglected in kidney transplant patients because of paucity of literature on the subject. Among various types of acid–base disorders, renal tubular acidosis (RTA) is the most frequently encountered disorder in renal transplant recipients. The prevalence of RTA varies from 12% to 58.1% in a review of 12 studies. In most of these studies, the serum HCO_3^- level was <22 mEq/L. Interestingly, metabolic acidosis develops at higher GFR levels in transplant patients compared to those with CKD who develop at lower GFRs.

Proximal RTA (type II) develops in approximately 19% of cases during the first 3 months of transplantation and then resolves spontaneously. This acid–base disorder is due to HCO_3^- wasting caused by ischemic tubular necrosis that is partially attributed to the harvest procedure. If proximal RTA develops after 2 years following transplantation, chronic rejection should be suspected. Distal RTA (type 1) is rather common. It may develop as early as the first 3 months and may last up to 9 years. Causes for its development include chronic rejection and calcineurin inhibitors (cyclosporine or tacrolimus). Tacrolimus seems to be the major reason for RTAs than cyclosporine.

Both proximal and distal RTAs can occur early after transplantation with spontaneous resolution of proximal RTA. Distal RTA can persist for long periods of time (up to 9 years). Alkali therapy is indicated for patients with distal RTA.

Type 4 RTA is seen most frequently with cyclosporine and tacrolimus use as well as other drugs that lower aldosterone levels.

The mechanisms for RTAs in kidney transplant patients are not completely understood, although immunologic mechanisms have been implicated. Also, calcineurin inhibitors seem to impair the activity of transporters involved in acid–base balance in the proximal and distal tubules. Appropriate treatment is recommended to prevent bone disease and other complications of metabolic acidosis.

Study Questions

Question 1 Which one of the following mechanisms is involved in the development of metabolic acidosis in patients with CKD stages 4 and 5?

A. Loss of HCO_3^- from extrarenal source
B. Hyperkalemia
C. Decreased serum phosphate levels
D. Decreased NH_4^+ excretion
E. All of the above

The answer is D. The important mechanism for development of metabolic acidosis in CKD stages 4/5 is decreased excretion of NH_4^+. However, titratable acidity remains either normal or slightly elevated. Thus, answer D is correct. Other remaining answers are incorrect.

Question 2 Which one of the following complications is expected to see in a patient with chronic metabolic acidosis?

A. Muscle wasting
B. Hypoalbuminemia
C. Progression of kidney disease
D. Development of bone disease
E. All of the above

The answer is E. All of the above complications develop in a patient with chronic metabolic acidosis. Thus, answer E is correct.

Question 3 Which one of the following serum HCO_3^- concentration in a CKD patient with metabolic acidosis warrants supplementation of oral bicarbonate?

A. <16 mEq/L
B. <18 mEq/L
C. <20 mEq/L
D. <22 mEq/L
E. <24 mEq/L

The answer is D. The 2013 KDIGO guidelines (see section "Suggested Reading") make the following statement regarding treatment of metabolic acidosis as "We suggest that in people with bicarbonate concentration <22 mmol/L treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated (2B)." Thus, answer D is correct.

Question 4 Which one of the following is the MOST common acid–base disorder in a patient with kidney transplantation?

A. High anion gap (AG) metabolic acidosis
B. Normal AG metabolic acidosis
C. Mixed acid–base disorder
D. Distal renal tubular acidosis (RTA)
E. Proximal RTA

The answer is D. Distal RTA (type 1) is rather common. It may develop as early as the first 3 months and may last up to 9 years. Causes for its development include chronic rejection and calcineurin inhibitors (cyclosporine or tacrolimus). Tacrolimus seems to be the major reason for RTAs than cyclosporine.

Proximal RTA (type II) develops in approximately 19% of cases during the first 3 months of transplantation and then resolves spontaneously. This acid–base disorder is due to HCO_3^- wasting caused by ischemic tubular necrosis that is partially attributed to the harvest procedure. If proximal RTA develops after 2 years following transplantation, chronic rejection should be suspected. Other acid–base disorders are uncommon. Thus, answer D is correct.

Case 1 You are following a 50-year-old nondiabetic man with eGFR of 24 mL/min, and his serum HCO_3^- concentration is 20 mEq/L despite daily oral $NaHCO_3$ dose of 96 mEq (12.5 g). His urine pH is 5.4. His only complaint is bloating of his stomach. Which one of the following is the MOST likely explanation for his low serum HCO_3^- concentration?

A. Noncompliance to $NaHCO_3$ ingestion
B. High protein (meat) intake
C. Low consumption of fruits and vegetables
D. All of the above
E. Progression of kidney disease due to metabolic acidosis

The answer is D. High acid load due to meat consumption, low consumption of fruits and vegetables, and probably noncompliance to full dose of alkali intake may have prevented improvement of his serum HCO_3^- concentration. It is unlikely that progression of kidney disease is the cause of his low serum HCO_3^- concentration. Thus, answer D is correct.

Question 5 Which one of the following foods provides low acid load (mEq/100 g edible food)?

A. Potatoes
B. Vegetables
C. Fruits
D. All of the above
E. Turkey

The answer is D. Potatoes (−4 mEq), vegetables (−2.8 mEq), and fruits (−3.1 mEq) provide base, causing alkalinity, and turkey provides 9.9 mEq of an acid load to blood. Thus, answer D is correct.

Question 6 Which of the following dietary consumptions predisposes a CKD patient with an eGFR of 70 mL/min to hyperchloremic metabolic acidosis?

A. Fruits and vegetables
B. High salt intake (>10 g/day)
C. Soy protein meat balls
D. Hazelnuts
E. Red wine (100 mL)

The answer is B. Except for salt, all other dietary consumptions provide precursors for base generation, whereas high salt (NaCl) intake provides high Cl^- that lowers serum HCO_3^- concentration with resultant hyperchloremic metabolic acidosis. It is similar to infusion of large quantities of normal saline to a patient with compromised renal function.

References

1. Abramowitz MK. Bicarbonate balance and prescription in ESRD. J Am Soc Nephrol. 2017;28:726–34.
2. Chen W, Abramowitz MK. Epidemiology of acid-base derangements in CKD. Adv Chronic Kidney Dis. 2017;24:280–8.
3. Wesson DE, editor. Metabolic acidosis. A guide to clinical assessment and management. New York: Springer; 2016.

Suggested Reading

Ambűhl PM. Posttransplant metabolic acidosis: a neglected factor in renal transplantation? Curr Opin Nephrol Hypertens. 2007;16:379–87.
Angélico LRN, de Souza GCA, Romão EA, et al. Alkaline diet and metabolic acidosis: practical approaches to the nutritional management of chronic kidney disease. J Renal Nutr. 2018;28:215–20.

Gennari FJ. Metabolic acidosis in chronic renal insufficiency. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 469–85.

Gennnari FJ, Negoi D. Acid-base considerations in end-stage kidney disease. In: Lerma EV, Weir MR, editors. Henrich's principles and practice of dialysis. 5th ed. Philadelphia: Wolters Kluwer; 2017. p. 419–35.

Goraya N, Wesson DE. Management of the metabolic acidosis of chronic kidney disease. Adv Chronic Kidney Dis. 2017;20:298–304.

Goraya N, Wesson DE. Clinical evidence that treatment of metabolic acidosis slows the progression of chronic kidney disease. Curr Opin Nephrol Hypertens. 2019;98:267–77.

Helderman JH, Schaefer H, Langone AJ, et al. Homeostasis of solute and water by the transplanted kidney. In: Alpern RJ, Moe OW, Caplan M, editors. Seldin and Giebisch's the kidney. Physiology and pathophysiology. 5th ed. San Diego: Academic Press (Elsevier); 2013. p. 3151–83.

Kovacic V, Roguljic L, Kovacic V. Metabolic acidosis of chronically hemodialyzed patients. Am J Nephrol. 2003;23:158–64.

Kraut JA, Madias NE. Metabolic acidosis of CKD: an update. Am J Kidney Dis. 2016;67:307–17.

Kraut JA, Madias NE. Adverse effects of the metabolic acidosis of chronic kidney disease. Adv Chronic Kidney Dis. 2017;24:289–97.

Mehrotra R, Kopple JD, Wolfson M. Metabolic acidosis in maintenance hemodialysis patients: clinical considerations. Kidney Int. 2003;64(Suppl 88):S13–25.

Messa PG, Alferi C, Vettoretti S. Metabolic acidosis in renal transplantation: neglected but of potential clinical relevance. Nephrol Dial Transplant. 2016;31:730–6.

Mujais S. Acid-base profile in patients on PD. Kidney Int. 2003;64(Suppl 88):S26–36.

Raphael K, Shihab FS. Acidosis and kidney allograft survival. J Am Soc Nephrol. 2017;28:1667–74.

Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc. 1995;95:791–7.

Remer T. Influence of diet on acid-base balance. Sem Dial. 2000;13:221–6.

Siener R. Dietary treatment of metabolic acidosis in chronic kidney disease. Nutrients. 2018;10:512,1–8.

Qian Q. Acid-base alterations in ESRD and effects of hemodialysis. Sem Dial. 2018;31:226–35.

Chapter 11
Metabolic Alkalosis

Metabolic alkalosis is defined as a primary increase in serum [HCO_3^-] >32 mEq/L with pH >7.45. Hypoventilation with an increase in arterial pCO_2 is an appropriate respiratory response for an increase in serum [HCO_3^-]. Thus, metabolic alkalosis is characterized by elevations in pH, [HCO_3^-] and pCO_2.

Metabolic alkalosis occurs very commonly in hospitalized patients. It accounts for about 50% of all acid–base disorders. Mortality rates approach 85% in patients with pH >7.65. pH of this extent occurs in combined metabolic and respiratory alkalosis, and recognition of this mixed acid–base disorder is extremely important to prevent morbidity and mortality in any patient.

Course of Metabolic Alkalosis

The course of metabolic alkalosis is divided into three phases: generation phase, maintenance phase, and recovery phase.

Generation Phase

Generation occurs either by loss of H^+ from the body or addition of alkali by any one of the causes shown in Table 11.1.

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_11

Table 11.1 Causes of metabolic alkalosis

Chloride-responsive alkalosis	Chloride-resistant alkalosis
Gastrointestinal (GI) and renal-associated	*Hypertension-associated*
Vomiting	Primary aldosteronism
Nasogastric suction	11β-hydroxysteroid dehydrogenase type 2 deficiency
Congenital chloride diarrhea	Licorice, chewing tobacco, carbenoxolone
Villous adenoma	Fludrocortisone administration
Posthypercapnia	Cushing syndrome
Cl^- -depletion alkalosis	Glucocorticoid-remediable aldosteronism
Cystic fibrosis	Hyperreninism and hyperaldosteronism (malignant and renovascular hypertension, renin-secreting tumors)
Severe K^+ deficiency	Liddle syndrome
Milk–alkali syndrome	*Normotension-associated*
Gastrocystoplasty	Bartter syndrome
Zollinger–Ellison syndrome	Gitelman syndrome
Drug-associated	*Others*
Loop diuretics	Hypercalcemia
Thiazide diuretics	Hypoparathyroidism
Poorly reabsorbable anions (carbenicillin, penicillin, phosphate, sulfate)	Post-feeding alkalosis
$NaHCO_3$ (baking soda)	
Sodium citrate, lactate, gluconate, acetate	
Antacids	
Transfusions	

Maintenance Phase

Following generation, persistence of metabolic alkalosis is maintained by volume depletion (Cl^--responsive), Cl^- deficiency, K^+ deficiency, reduced glomerular filtration rate (GFR), or excess mineralocorticoid activity.

Cl^- depletion sustains metabolic alkalosis by the following mechanisms (Fig. 11.1):

1. Cl^- depletion inhibits K^+ reabsorption in the thick ascending limb of Henle's loop (TALH) via Na/K/2Cl cotransporter
2. Along with K^+, Na^+ reabsorption is also impaired in the TALH. This causes more delivery of Na^+ to the cortical collecting duct (CCD), where it is reabsorbed via the luminal epithelial Na^+ channel (ENaC). Reabsorption of Na creates a negative lumen potential, resulting in K^+ and H^+ secretion

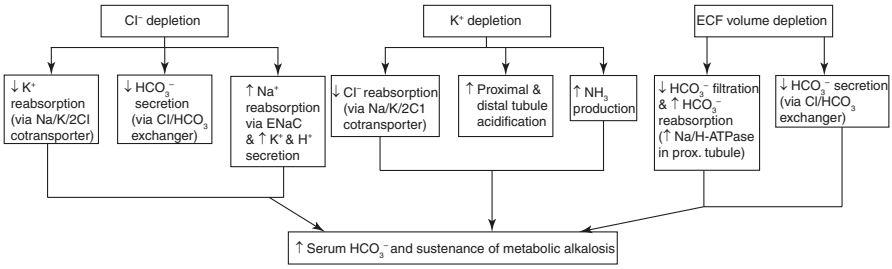
Cl⁻ depletion
K⁺ depletion
ECF volume depletion
↓ K⁺ reabsorption (via Na/K/2Cl cotransporter)
↓ HCO3⁻ secretion (via Cl/HCO3 exchanger)
↑ Na⁺ reabsorption via ENaC & ↑ K⁺ & H⁺ secretion
↓ Cl⁻ reabsorption (via Na/K/2C1 cotransporter)
↑ Proximal & distal tubule acidification
↑ NH3 production
↓ HCO3⁻ filtration & ↑ HCO3⁻ reabsorption (↑ Na/H-ATPase in prox. tubule)
↓ HCO3⁻ secretion (via Cl/HCO3 exchanger)
↑ Serum HCO3⁻ and sustenance of metabolic alkalosis

Fig. 11.1 Factors that generate and maintain metabolic alkalosis

3. Cl^- depletion causes decreased delivery of Cl^- to the CCD where HCO_3^- secretion is reduced via apical Cl/HCO_3 exchanger located in the intercalated type B cell. Thus, Cl^- depletion maintains metabolic alkalosis by causing hypokalemia and hyperbicarbonatemia

K^+ depletion maintains metabolic alkalosis by the following mechanisms (Fig. 11.1):

1. A decrease in intracellular pH due to movement of H^+ into the cell to replace K^+ loss
2. An increase in HCO_3^- reabsorption by enhanced activities of luminal Na/H-ATPase and basolateral Na/HCO_3 cotransporters in the proximal tubule
3. An increase in distal tubule acidification by activating H-ATPase in response to increased production of NH_3
4. A decrease in Na/K/2Cl cotransporter activity due to Cl^- depletion in the TALH
5. Reduction of GFR by both K^+ and Cl^- depletion

Recovery Phase Correction of Cl^-, K^+, and treatment of underlying cause improves metabolic alkalosis.

Figure 11.1 summarizes the mechanisms for generation and maintenance of metabolic alkalosis. Cl^- loss with Na^+ induces volume contraction. Also, Cl^- depletion causes K^+ loss. Therefore, NaCl administration corrects certain cases of metabolic alkalosis. Mineralocorticoid excess stimulates Na^+ reabsorption and, in turn, promotes K^+ and H^+ secretion. Volume status is variable (↑ in primary aldosteronism and ↓ in Gitelman syndrome).

Respiratory Response to Metabolic Alkalosis An increase in pCO_2 due to hypoventilation is a normal response to metabolic alkalosis, so that extremely dangerous levels of blood pH are avoided. On average, pCO_2 increases by 0.7 mmHg (above normal pCO_2 of 40 mmHg) for each mEq/L increase in serum $[HCO_3^-]$ (above normal $[HCO_3^-]$ of 24 mEq/L). The following example shows the appropriate respiratory response to an increase in pCO_2 in metabolic alkalosis.

Example

	pH	HCO_3^-	pCO_2
Normal:	7.40	24 mEq/L	40 mmHg
Patient:	7.47	34 mEq/L	?

$$\Delta HCO_3^- = 34 - 24 = 10$$
$$\text{Expected } pCO_2 = 10 \times 0.7 = 7$$
$$40 + 7 = 47$$

Classification

Clinically, metabolic alkalosis is divided into:

1. Chloride (saline)-responsive alkalosis
2. Chloride (saline)-resistant alkalosis

Causes

The most important causes of metabolic alkalosis are shown in Table 11.1.

Pathophysiology

For simplicity, the pathophysiology of metabolic alkalosis is discussed in selective conditions and under two major mechanisms: renal and gastrointestinal (GI).

Renal Mechanisms

Renal Transport Mechanisms

Since retention of HCO_3^- and secretion of H^+ are responsible for development of metabolic alkalosis, it is important to recall the normal cellular mechanisms involved in their renal handling. Disturbances in these transport mechanisms cause metabolic alkalosis by retention of HCO_3^- and secretion of H^+. Table 11.2 summarizes the transport mechanisms and their modifiers for HCO_3^- reabsorption and sustenance of metabolic alkalosis. Figure 11.2 shows mutations of some of the transporters that result in genetic diseases and metabolic alkalosis.

Table 11.2 Renal mechanisms for increased HCO_3^- reabsorption

Tubule	Transporter	Mechanism for HCO_3^- reabsorption
PT	Na/H-ATPase	↓ K^+ stimulates H^+ secretion
	H-ATPase	↓ K^+ stimulates H^+ secretion
TALH	Na/K/2Cl cotransporter	1. ↑ Delivery of NaCl to CCD, resulting in ↑ Na^+ reabsorption with subsequent ↑ K^+ and H^+ secretion due to loop diuretic-inhibition of cotransporter
		2. Bartter syndrome due to mutation in cotransporter
		3. ↓ K^+ inhibition of cotransporter
		4. Cl^- depletion by above mechanisms
DCT	Na/Cl cotransporter	1. ↑ Delivery of NaCl to CCD, resulting in ↑ Na^+ reabsorption with subsequent ↑ K^+ and H^+ secretion due to thiazide diuretic-inhibition of cotransporter
		2. ↓ K^+ inhibition of cotransporter
		3. Gitelman syndrome due to mutation in cotransporter
CCD		
Principal cell	ENaC	Liddle syndrome due to mutation in ENaC
β-intercalated cell	Pendrin (Cl/HCO_3 exchanger)	1. Hypokalemia downregulates pendrin, resulting in maintenance of metabolic alkalosis
		2. Loss-of-function mutation of gene encoding pendrin aggravates metabolic alkalosis
		3. Thiazide therapy aggravates metabolic alkalosis in Pendred syndrome
α-intercalated cell	H-ATPase	↑ H^+ secretion in response to ↑ Na^+ delivery to ENaC due to loop diuretics, Bartter syndrome, and Gitelman syndrome
	H/K-ATPase	Same as above

PT proximal tubule, *TALH* thick ascending limb of Henle's loop, *DCT* distal convoluted tubule, *CCD* cortical collecting duct, ↑ increase, ↓ decrease

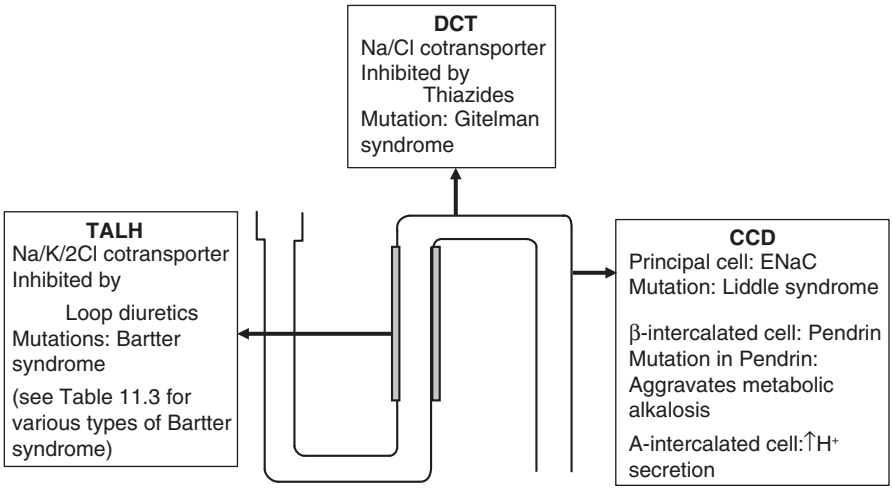

Fig. 11.2 Mutations of transporters in various segments of the nephron. TALH thick ascending limb of Henle's loop; DCT distal convoluted tubule; CCD cortical collecting duct

Genetic Mechanisms

Bartter syndrome It is caused by genetic defects in the apical or basolateral membrane transport mechanisms of the thick ascending limb of Henle's loop. Various types of Bartter syndrome are shown in Table 11.3.

- In general, patients with Bartter syndrome behave similar to patients on loop diuretics.
- Generation phase is due to increased loss of H^+ in the urine.
- Maintenance phase is due to K^+ and Cl^- loss, volume depletion, and secondary hyperaldosteronism.
- Characterized by hypokalemia, metabolic alkalosis, and normal blood pressure or at times hypotension.
- Treatment includes chronic supplementation of K^+. Spironolactone, amiloride, ACE-inhibitors, and nonsteroidal anti-inflammatory drugs have been tried with variable results.

Gitelman syndrome It is caused by mutations in distal tubule Na/Cl cotransporter.

- Behaves similar to a patient on thiazide diuretic.
- Characterized by hypokalemia, hypomagnesemia, metabolic alkalosis, and normal or low blood pressure. Although these manifestations are similar to Bartter

Table 11.3 Inherited disorders of NaCl transport mechanisms in various segments of the nephron

Segment and involved transporter	Disease	Some clinical features	Inheritance
Thick ascending limb			
Apical Na/K/2Cl cotransporter	Neonatal Bartter syndrome type 1	Hypokalemia, metabolic alkalosis, hypercalciuria, hypotension	AR
Apical K channel (ROMK)	Neonatal Bartter syndrome type 2	Hypokalemia, metabolic alkalosis, hypotension	AR
Basolateral Cl channel (ClC-kb)	Classic Bartter syndrome type 3 (infantile)	Hypokalemia, metabolic alkalosis, hypotension or normal BP	AR
Basolateral Cl channel (ClC-kb/barttin)	Bartter syndrome type 4	Hypokalemia, metabolic alkalosis, hypotension, sensorineural deafness	AR
Activation of basolateral Ca^{2+}-sensing receptor	Bartter syndrome type 5	Salt wasting, hypokalemia, metabolic alkalosis, hypercalciuria	AD
Distal convoluted tubule			
Apical Na/Cl cotransporter	Gitelman syndrome	Hypokalemia, metabolic alkalosis, hypocalciuria, normal to low BP	AR
Cortical collecting duct			
Apical epithelial Na^+ channel (ENaC)	Liddle syndrome	Hypokalemia, metabolic alkalosis, low rennin and aldosterone levels, hypertension (responsive to amiloride)	AD

↑ increase, ↓ decrease, *AD* autosomal dominant, *AR* autosomal recessive, *ROMK* renal outer medullary potassium channel

syndrome, Gitelman syndrome occurs at any age (1–70 years) but is diagnosed in young adults.
- Generation and maintenance phases are similar to those of Bartter syndrome.
- The only way one can distinguish Gitelman syndrome from Bartter syndrome is urinary Ca^{2+} excretion. In Gitelman syndrome, urinary excretion of Ca^{2+} is *low* (hypocalciuria), whereas in Bartter syndrome it is *normal* or *high* (hypercalciuria).
- Hypocalciuria is due to proximal tubule reabsorption of Ca^{2+}, and hypomagnesemia is probably related to downregulation of Mg^{2+} channel in the distal collecting tubule.
- Treatment includes lifelong liberal salt intake, K^+, and Mg^{2+} supplementation (KCl, $MgCl_2$) as well as K^+-sparing diuretics (spironolactone, amiloride, spironolactone-receptor blocker).

Liddle syndrome An autosomal dominant disorder is caused by mutations in the subunits of ENaC.

- Generation of metabolic alkalosis is caused by increased K^+ and H^+ loss, and maintenance is due to hypokalemia and hypochloremia.
- Aldosterone levels are low because of Na^+ reabsorption and volume expansion.
- Characterized by hypokalemia, metabolic alkalosis, and hypertension.
- Hypertension does not respond to spironolactone. Amiloride is the drug of choice.

Glucocorticoid-remediable hyperaldosteronism (GRA) It is also called familial hyperaldosteronism type 1.

- Caused by fusion of two enzymes: aldosterone synthase and 11β-hydroxylase.
- Patients present with hypokalemia, metabolic alkalosis, and hypertension.
- Administration of glucocorticoid improves hypokalemia, metabolic alkalosis, and hypertension.

Apparent mineralocorticoid excess syndrome (AME) Cortisol is not converted into inactive cortisone by the mutated enzyme 11β-hydroxysteroid dehydrogenase type 2.

- Patients present with hypokalemia, metabolic alkalosis, and hypertension.
- Treatment with spironolactone or amiloride improves hypokalemia, alkalosis, and hypertension.
- AME can also be acquired. Ingestion of licorice, chewing tobacco, bioflavonoids, or carbenoxolone can cause AME. These agents contain glycyrrhetinic acid, which is a competitive inhibitor of 11β-hydroxysteroid dehydrogenase type 2.
- Clinical manifestations are similar to the genetic type of AME.

Acquired Causes

Primary aldosteronism It is caused by autonomous secretion of aldosterone by adrenal adenoma or hyperplasia of the adrenal gland.

- Alkalosis is generated by K^+ and H^+ loss due to increased delivery of NaCl to the distal nephron.
- Hypokalemia, hypochloremia, and persistent aldosterone activity maintain metabolic alkalosis.
- Characterized by hypokalemia, hypertension, and metabolic alkalosis.
- Removal of adenoma or treatment with K^+-sparing diuretics (spironolactone) corrects metabolic abnormalities and hypertension.

Malignant hypertension A disorder of high renin-AII-aldosterone activity.

- Characterized by hypertension, hypokalemia, and metabolic alkalosis
- *Renal artery stenosis*: Clinically similar to malignant hypertension with high renin-AII-aldosterone activity.
- Patients present with severe hypokalemia, hypertension, and metabolic alkalosis.
- Removal of stenosis by stents or surgery improves hypokalemia, metabolic alkalosis, and hypertension.

Drugs other than diuretics Exogenous alkali causes metabolic alkalosis only when the subject is hypovolemic with compromised renal function. Dialysis patients develop metabolic alkalosis due to the use of HCO_3^- in the dialysate bath.

- One study showed that daily ingestion of 140 g (1667 mEq) of baking soda ($NaHCO_3$) for up to 3 weeks raises serum [HCO_3^-] and causes metabolic alkalosis.
- Metabolic alkalosis resolves following discontinuation of $NaHCO_3^-$ provided hypokalemia and volume depletion are absent; however, it continues once renal failure develops.
- Delivery of nonreabsorbable anions such as sodium penicillin to the distal tubule promotes K^+ secretion, resulting in hypokalemia and metabolic alkalosis.

Diuretics Diuretics other than acetazolamide and K^+-sparing diuretics generate metabolic alkalosis.

- Mechanisms include:

  1. Relative volume depletion by loss of NaCl
  2. Hypokalemia
  3. Hypochloremia
  4. Increased net acid secretion due to hyperaldosteronism (most important)

- Note that urine Cl^- may be variable; high when diuretic action is maximum and low after 24 h of diuretic ingestion.

Posthypercapnic metabolic alkalosis This condition results in patients with chronic respiratory acidosis with high HCO_3^- and pCO_2. When such patients require intubation, and pCO_2 is acutely lowered, blood pH goes up without a change in serum [HCO_3^-].

- Since the kidneys cannot excrete HCO_3^- immediately, the pH should be corrected by any one or all of the following treatments:
  1. Increase pCO_2
  2. Lower serum [HCO_3^-] by administration of normal saline and/or acetazolamide
  3. To lower pH acutely, some physicians use HCl administration, but this option is rarely required

Milk (calcium)–alkali syndrome This syndrome was initially described in patients with peptic ulcer disease who consumed calcium salts and milk for many years. With the introduction of new drugs for peptic ulcer disease, the use of calcium salts and milk has decreased substantially. However, calcium salts alone or in combination with vitamin D are being used to prevent and/or treat osteoporosis. Thus, the incidence of milk–alkali syndrome is increasing recently.

- Since milk is not consumed to prevent peptic ulcer or bone disease, and calcium supplements are recommended, the preferable term may be *calcium–alkali* syndrome.
- Calcium–alkali syndrome is characterized by the triad of hypercalcemia, metabolic alkalosis, and some degree of renal insufficiency. Hypercalcemia impairs PTH secretion, which subsequently enhances proximal tubular HCO_3^- reabsorption. Also, hypercalcemia has effects similar to loop diuretics in the thick ascending limb of Henle's loop by activating basolateral Ca^{2+}-sensing receptor. This activation causes loss of Na^+, K^+, and Cl^- with resultant volume contraction. Both development and maintenance of metabolic alkalosis occur because of continued intake of alkali and its limited excretion due to volume depletion.
- Hydration with normal saline initially will improve both calcium and metabolic alkalosis, but elevated creatinine may persist. Discontinuation of alkali and calcium will also improve metabolic alkalosis.

Hypercalcemia Hypercalcemia due to increased bone resorption, as in malignancy or other conditions, may cause metabolic alkalosis. Increased bone resorption releases alkali (calcium carbonate), which is reabsorbed by the proximal tubule by hypercalcemia-suppressed PTH action. Also, HCO_3^- excretion is reduced due to volume contraction. Also, hypercalcemia can directly stimulate H^+ secretion with resultant increase in net acid excretion. As mentioned above, hypercalcemia has loop diuretic-like effect. Thus, hypercalcemia per se can cause metabolic alkalosis.

Cystic fibrosis Metabolic alkalosis develops in patients with cystic fibrosis due to volume depletion and hypokalemia. Loss of Na^+ and Cl^- in sweat causes volume depletion and hypochloremia. Hyperaldosteronism due to volume depletion results in hypokalemia. H^+ secretion also increases. All these changes generate and maintain metabolic alkalosis.

Table 11.4 summarizes various laboratory tests that are useful in the differential diagnosis of metabolic alkalosis.

Table 11.4 Serum renin, aldosterone (Aldo), urine electrolytes, and pH in metabolic alkalosis

Condition	Renin	Aldo	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	pH	Volume status
Bartter syndrome	↑	↑	↑	↑	↑	↓	↓ (acid)	↓
Gitelman syndrome	↑	↑	↑	↑	↑	↓	↓	↓
Liddle syndrome	↓	↓	N↑	↑	↑	↑	↓	↑
Licorice	↓	↓	↑	↑	↑	↓	↓	↑
AME	↓	↓	↑	↑	↑	↓	↓	↑
GRA	↓	↑	↑	↑	↑	↓	↓	↑
Primary aldosteronism	↓	↑	↑	↑	↑	↓	↓	↑
Malignant and renovascular HTN	↑	↑	↑	↑	↑	↓	↓	↓
Diuretics (loop and thiazide)	↑	↑	↓↑[a]	↑	↑	↓	↓	↓

AME apparent mineralocorticoid excess syndrome, *GRA* glucocorticoid-remediable hyperaldosteronism, *N* normal, ↑ increase, ↓ decrease
[a]Variable

GI Mechanisms

Vomiting and Nasogastric Suction

This is one of the most common causes of metabolic alkalosis besides diuretic use.

- On average, gastric fluid contains the following electrolytes in mEq/L:

$$H^+ = 100$$
$$Cl^- = 120$$
$$Na^+ = 15$$
$$K^+ = 10$$
$$\text{Volume} = 1\text{L}$$

- Generation of alkalosis starts with loss of HCl, resulting in addition of HCO_3^- and loss of Cl^-.
- Glomerular filtration of Cl^- is reduced.
- Initially, the kidney gets rid of HCO_3^-, which obligates Na^+ and K^+ excretion.
- Because of bicarbonaturia, the urine pH is alkaline (>6.5).
- If vomiting or gastric suction continues, loss of Na^+ and water results in volume depletion. Na^+ and HCO_3^- reabsorption increases, and their excretion is decreased.
- Na^+ reabsorption is accompanied by secretion of H^+ and K^+, resulting in net acid excretion, and urine pH becomes acidic.
- Metabolic alkalosis is, therefore, maintained by hypokalemia and volume depletion.

Table 11.5 Urinary electrolyte (mEq/L) pattern and pH in vomiting

Vomiting	Na^+	K^+	Cl^-	HCO_3^-	pH
Early (1–2 days)	↑	↑	↓	↑	↑
Late (>2 days)	↓	↑	↓	↓	↓

- Table 11.5 shows urinary electrolyte pattern in early (1–2 days) and late (>2 days) vomiting.
- Treatment: Both volume repletion with normal saline and correction of hypokalemia with KCl improve metabolic alkalosis.
- Correction of the cause of vomiting should be addressed to prevent metabolic alkalosis.
- Urine Cl^- > 40–50 mEq/L and urine pH >6.5 during treatment are indications of volume expansion as well as improvement in metabolic alkalosis.

Congenital Chloridorrhea

This is inherited as an autosomal recessive disease.

- Cl^- absorption in the ileum and colon is decreased due to mutations in the Cl/HCO_3 exchanger, resulting in stool loss of Cl^-.
- Extremely large fecal losses of Na^+, K^+, and water result in hypokalemia, volume depletion, and metabolic alkalosis.
- Secondary hyperaldosteronism increases body volume by Na^+ and water reabsorption while promoting maintenance of alkalosis by secretion of K^+ and H^+.
- Urinary Cl^- and K^+ levels are low because of their loss in the stool.
- Neonatal abdominal distention due to intestinal dilatation and maternal polyhydramnios are the clues to the diagnosis of this disease.

Villous Adenoma

Metabolic acidosis is common; however, some patients develop metabolic alkalosis.

- Fecal loss of NaCl, HCO_3^- and water seems to generate and maintain metabolic alkalosis.

Laxative Abuse

Similar to villous adenoma, laxative abuse causes hyperchloremic metabolic acidosis. However, some case reports documented metabolic alkalosis simulating Bartter syndrome.

- Urine Cl^- and K^+ are low.
- Hydration with NaCl, K^+ supplementation, and discontinuation of laxative improve metabolic alkalosis.

Clinical Manifestations

Severe metabolic alkalosis affects several organ systems, including central nervous system, neuromuscular, cardiovascular, and pulmonary systems. In addition, several metabolic abnormalities have been reported. Table 11.6 summarizes these manifestations.

Diagnosis

Step 1

- History of diuretic use, exogenous intake of antacids, Ca^{2+} supplements, laxatives, licorice, and inquiries into vomiting or bulimia, family, or personal history of hypertension are extremely important.
- Complaint of alternating diarrhea and constipation is suggestive of laxative abuse.

Table 11.6 Clinical manifestations of metabolic alkalosis

Central nervous system
Reduction in blood flow
Confusion
Obtundation
Reduced seizure threshold
Neuromuscular
Increased excitability
Tetany
Cardiovascular
Reduced cardiac output
Reduced coronary blood flow
Arteriolar vasoconstriction
Increased heart rate
Predisposition to refractory ventricular and supraventricular arrhythmias
Pulmonary
Hypoventilation
Hypercapnia
Hypoxia
Metabolic
Hypokalemia
Decreased ionized Ca^{2+}
Hypophosphatemia
Hypomagnesemia
Stimulation of glycolysis and production of lactate

Step 2

- Physical examination includes:
  1. Blood pressure
  2. Volume status
  3. Examination of teeth enamel (usually black due to gastric HCl)
  4. Examination of dorsum of hand for scarring and hypertrophy of salivary glands (habitual vomiting)
  5. Peripheral edema in young women unrelated to pregnancy and menstruation (suspect diuretic use for idiopathic edema)

Step 3

- Laboratory tests:
  - Serum electrolytes, including creatinine, BUN, Ca^{2+}, Mg^{2+}, phosphate, and albumin.
  - ABG to exclude chronic respiratory acidosis.
  - Urine electrolytes and pH (see Tables 11.4 and 11.5).
  - Of all urine electrolytes, urine Cl^- is the most important electrolyte that distinguishes Cl^--responsive from Cl^--resistant alkalosis.
- Figure 11.3 illustrates the use of urine Cl^- determination in the evaluation of metabolic alkalosis.

Serum anion gap (AG) is increased in metabolic alkalosis due to (1) an increase in albumin with negative charge on it and (2) an increase in glycolysis due to stimulation of the rate-limiting enzyme, phosphofructokinase, and lactic acid production. Although the AG up to 8 mEq/L has been observed, its clinical importance has never been appreciated in metabolic alkalosis.

Treatment

Treatment includes:

1. Address the specific cause and correct it
2. Volume depletion: Common in many patients with metabolic alkalosis. Administration of normal saline is the appropriate therapy in such patients. It replaces volume and Cl^- loss
3. Administer KCl orally or i.v. for severe hypokalemia
4. Avoid Ringer's lactate, as lactate is converted into HCO_3^- and worsens alkalosis
5. Intravenous HCl (0.1 or 0.2 M) is indicated when NaCl and KCl administrations are contraindicated, blood pH >7.5 or hypervolemic

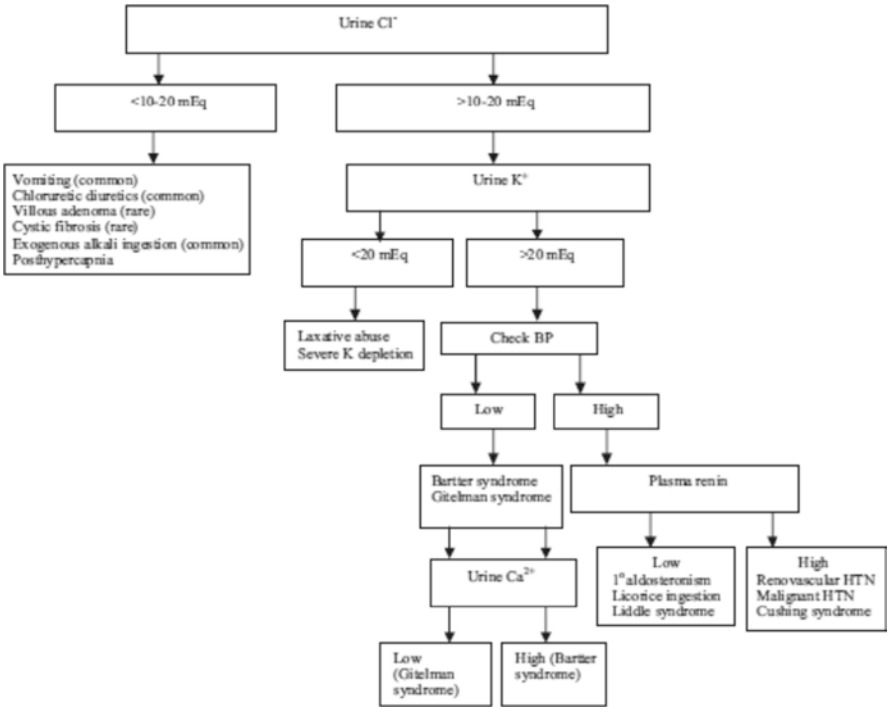

Fig. 11.3 Evaluation of metabolic alkalosis

6. HCl should be infused via a large vein to avoid extravasation at <0.2 mEq/kg/h. Amount of HCl needed to lower serum [HCO_3^-] from 40 to 34 mEq/L is calculated as follows:

$$\text{Weight } (\text{kg}) = 70$$
$$\text{H}^+ \text{ space} = 50\%$$
$$\Delta \text{HCO}_3^- = 6(\text{decrement from 40 to 34 mEq/L})$$
$$70 \times 0.5 \times 6 = 210 \text{ mEq}$$

7. An alternative to HCl is NH_4Cl or arginine HCl. NH_4Cl is contraindicated in hepatic and renal failure
8. Acetazolamide (250 mg BID or TID) is used to improve metabolic alkalosis in patients with volume overload and normal renal function
9. When a renal failure patient fails to respond to Cl^- repletion, renal replacement therapy (hemodialysis, peritoneal dialysis, or hemodiafiltration) is indicated
10. Occasionally, in patients with protracted vomiting or prolonged nasogastric suction, H_2-blockers such as cimetidine or ranitidine, or H/K-ATPase inhibitor such as omeprazole can blunt acid production in the stomach and reduce HCl loss

11. Omeprazole is effective in the treatment of alkalosis in patients with gastrocystoplasty
12. Octreotide is used to control hypergastrinemia in Zollinger–Ellison syndrome

Study Questions

Case 1 A 42-year-old man is admitted for dizziness and weakness. His blood pressure is 120/80 mmHg with a pulse rate of 90 beats per minute (sitting), and 100/64 mmHg with a pulse rate of 110 beats per minute (standing). He is not on any medications, but admits to vomiting. Admitting laboratory data

Electrolytes	ABG
Na^+ = 129 mEq/L	pH = 7.53
K^+ = 2.5 mEq/L	pCO_2 = 63 mmHg
Cl^- = 58 mEq/L	HCO_3^- = 57 mEq/L
HCO_3^- = 58 mEq/L	
Creatinine = 1.9 mg/dL	
BUN = 32 mg/dL	
Glucose = 94 mg/dL	

Question 1 Analyze the acid–base disturbance.

Answer To analyze this acid–base disorder, follow the steps 1–5 shown in Chap. 4.

Step 1 According to the Henderson equation, the $[H^+]$ is 26, which corresponds to a pH of 7.53. Therefore, the reported pH is correct.

Step 2 Based on elevated pH and serum $[HCO_3^-]$, the primary acid–base disturbance is metabolic alkalosis.

Step 3 The AG is 13, which is slightly elevated due to alkalemia.

Step 4 The cause for metabolic alkalosis is vomiting.

Step 5 The respiratory compensation is appropriate, suggesting that this acid–base disturbance is an uncomplicated metabolic alkalosis.

Question 2 What other laboratory test should you order?

Answer The laboratory test that is pertinent to this acid–base disorder is determination of urinary Cl^-, which is 5 mEq/L. The patient, therefore, has Cl^--responsive metabolic alkalosis.

Question 3 Why did the patient develop hypokalemia, if he had only vomiting?

Answer There are two mechanisms for hypokalemia: (1) volume depletion-induced hyperaldosteronism, and (2) adequate delivery of Na^+ with HCO_3^- to the cortical collecting duct where Na^+ is reabsorbed and K^+ is secreted.

Question 4 How would you treat this acid–base disturbance?

Answer The patient is volume-depleted with orthostatic blood pressure and pulse changes. The appropriate i.v. fluid is normal (0.9%) saline with K^+ supplementation, which replenishes both volume and Cl^-.

Case 2 The patient is a 65-year-old man who was brought to the Emergency Department (ED) after being found on the floor at home due to a fall. He was awake and alert but oriented to place and time only. He was then noted to have a draining wound of his left foot that was wrapped in plastic. The patient complained of generalized weakness with muscle cramps and poor appetite for a few days. He also admitted to difficulty in walking from his foot ulcer. While in the ED, the patient became agitated, requiring intubation for airway protection. Past medical history included only foot ulcers for 2 years. He was hospitalized 2 weeks prior to this admission at another hospital. He was treated with intravenous antibiotics for 1 week and discharged. He was not on any medications.

On admission, his blood pressure was 131/77 mmHg with a regular pulse rate of 82 per minute. He was afebrile. His body mass index was 18.2. He was well developed but poorly nourished. Except for a well-demarcated left lower foot ulcer with unclean margins extending from distally one-third of foot to toes, the rest of the physical examination was unremarkable. The ulcers were foul-smelling with serous but not purulent discharge, and wrapped with white powder in plastic cover.

Laboratory value	Day 1	Day 2	Day 3	Day 4	Day 5
Na^+ (mEq/L)	148	142	140	137	138
K^+ (mEq/L)	1.8	2.9	2.9	2.5	3.6
Cl^- (mEq/L)	73	92	92	96	100
HCO_3^- (mEq/L)	54	45	40	38	32
Creatinine (mg/dL)	3.4	2.7	2.4	1.6	1.2
Albumin (g/dL)	2.7	–	–	–	–
Lactate (mmol/L)	2.2	–	–	–	–
Urine (U) pH	6.0	6.0	–	8.0	–
U_{Na} (mEq/L)	21	27	43	74	–
U_K (mEq/L)	58	90	59	4	–
U_{Cl} (mEq/L)	<10	<10	26	37	–
Ketones	Negative	–	–	–	–
ABG					
pH	7.69	7.55	7.48	7.48	7.46

Laboratory value	Day 1	Day 2	Day 3	Day 4	Day 5
pCO_2	45	56	59	51	34
pO_2	48	218	134	101	94
CK (U)	5604	1846	1335	771	–
Tropinin	28.32	5.16	–	–	–

Chest X-ray was unremarkable. The EKG showed normal sinus rhythm with pulse rate of 80 beats per minute, normal axis, 1st degree AV block, QT prolongation (536 ms), 1 VPC, ST depression in V3–V6, and inferior leads. Because of agitation, a CT scan of head was done, which was negative. Initial and subsequent laboratory data are as follows:

Question 1 What is the acid–base disturbance on day 1?

Answer Based on elevated pH and HCO_3^-, the primary acid–base disorder is metabolic alkalosis.

Question 2 What other acid–base disorders are present?

Answer Calculation of respiratory compensation and AG would help to characterize the acid–base disturbance in this patient. From Table 4.13, it is evident that the expected pCO_2 should be 61; however, the reported pCO_2 is 45. This indicates that the patient is hyperventilating and, therefore, respiratory alkalosis is also present.

The AG is 21, which is not entirely due to metabolic alkalosis. Despite volume depletion, his albumin is only 2.7 g/dL, which could not account for elevated AG. Also, ketoacidosis or lactic acidosis is not the cause. We believe that either renal insufficiency or other organic acid may have caused elevated AG.

Thus, the acid–base disorder is a primary metabolic alkalosis with superimposed respiratory alkalosis and a high AG metabolic acidosis.

Question 3 What would have been his pH, if his pCO_2 were 61 mmHg?

Answer If the patient had a pCO_2 of 61, his pH would have been 7.53 instead of 7.69 (calculation based on Henderson equation and assuming serum HCO_3^- of 54 mEq/L).

Question 4 Based on urine electrolytes, what is your differential diagnosis?

Answer Based on low urine Cl^-, the patient has Cl^--responsive metabolic alkalosis. Vomiting, thiazide diuretic use, milk–alkali syndrome (although serum Ca^{2+} was 8.2 mg/dL), or exogenous alkali intake were considered.

Urine Cl^- is always low in both early and late vomiting, but its level is usually high in recent diuretic use and relatively low in remote use. Urine pH is alkaline in early vomiting, but acidic in late vomiting and diuretic use. Based on urine

electrolytes, we excluded the diagnosis of diuretic use in our patient. However, low urine Na^+, high K^+, low Cl^-, and acidic pH are consistent with late vomiting. Milk–alkali syndrome was ruled out when previous serum creatinine of 0.8 mg/dL was available later that day. Thus, either habitual vomiting or exogenous alkali intake was considered initially in our patient.

Question 5 How would you manage the patient?

Answer First, normal saline with KCl supplementation is needed to improve volume status and serum [K^+]. Volume expansion improves GFR and promotes HCO_3^- excretion. Second, acetazolamide (250 or 500 mg QD or BID) can be tried. Third, HCl administration can be considered, if there is no improvement in pH despite volume and K^+ correction. Fourth, cardiology consult, and finally, adequate oxygenation and trial of extubation.

In a 24-h period, the patient received a total of 7 L of 0.9% saline, 2 L of 0.45% saline, 360 mEq of KCl, and 8 mEq of $MgSO_4$. BP improved. The patient received only one dose of acetazolamide 250 mg, after adequate hydration. In a 4-day period, the patient received a total of 7 L of 0.9% saline, 19 L of 0.45% saline, and 960 mEq of KCl. The EKG abnormalities had resolved, and an ECHO showed no wall motion or valvular abnormalities.

Question 6 What is the final diagnosis?

Answer After extubation, the patient admitted to eating baking soda (a palm full with water) and covering the foot ulcer with adequate amount of baking soda for a year and a half. The final diagnosis was severe metabolic alkalosis as a primary acid–base disorder due to chronic ingestion of baking soda ($NaHCO_3$).

Case 3 A 17-year-old Caucasian medical student is seen in the ED for persistent headache for a 2-week duration. She has no history of hypertension, migraine, or diabetes. She has been healthy and not on any medication. There is no family history of hypertension other than obesity. Physical examination shows a blood pressure of 200/142 mmHg and pulse rate of 94 beats per minute. Her BP was normal 6 months ago. Funduscopic examination reveals hypertensive retinopathy without papilledema. There are no crackles, S_4 or S_3, abdominal bruits, or edema. Neurologic examination is normal. Laboratory data:

Serum	Urine
Na^+ = 136 mEq/L	pH = 6.2
K^+ = 2.8 mEq/L	Osmolality = 1000 mOsm/kg H_2O
Cl^- = 84 mEq/L	Na^+ = 80 mEq/L
HCO_3^- = 35 mEq/L	K^+ = 55 mEq/L
Creatinine = 1.5 mg/dL	Cl^- = 75 mEq/L
BUN = 32 mg/dL	

Serum	Urine
Glucose = 92 mg/dL	
Albumin = 4.2 g/dL	
ABG: pH = 7.48 pCO_2 = 47 mmHg HCO_3^- = 34 mEq/L	

Question 1 What is the acid–base disturbance?

Answer Both blood pH and serum [HCO_3^-] are increased; therefore, the primary acid–base disturbance is metabolic alkalosis with appropriate respiratory response.

Question 2 What is the significance of the urine Cl^-?

Answer Urine Cl^- determination is very important to distinguish Cl^--responsive from Cl^--resistant metabolic alkalosis. This patient has Cl^--resistant metabolic alkalosis.

Question 3 What is the differential diagnosis of her metabolic alkalosis with hypertension?

Answer From Table 11.1, the causes of Cl^--resistant metabolic alkalosis with hypertension are:

1. Primary aldosteronism
2. 11β-hydroxysteroid dehydrogenase type 2 deficiency
3. Licorice, chewing tobacco, carbenoxolone
4. Fludrocortisone administration
5. Cushing syndrome
6. Glucocorticoid-remediable aldosteronism
7. Hyperreninism and hyperaldosteronism (malignant and renovascular hypertension, renin-secreting tumors)
8. Liddle syndrome

Question 4 What tests would you order to distinguish the above clinical syndromes?

Answer Plasma renin and aldosterone levels are very helpful. Both of them are high.

Question 5 What is the diagnosis in this patient?

Answer Malignant hypertension is unlikely in view of normal blood pressure 6 months ago. Although retinopathy supports the diagnosis of long-standing

hypertension, the absence of papilledema does not support the diagnosis of malignant hypertension.

Renin-secreting tumor is a possibility, however, patients with this tumor have resistant hypertension prior to diagnosis of this tumor. Although the occurrence of this tumor in many case reports is in young patients (18–24 years), they all had prior hypertension. Also, retinopathy has not been described (to my knowledge). After exclusion of the above conditions, possible renovascular hypertension has been entertained.

Question 6 What diagnostic test would you order to confirm renovascular hypertension?

Answer After volume expansion and controlling BP, an MR angiography is preferred because of its 100% sensitivity and 94% specificity for detecting renovascular stenosis.

This patient was found to have unilateral renal artery stenosis due to fibromuscular dysplasia.

Case 4 A 22-year-old woman visits her primary care physician for weakness, fatigue, and occasional dizziness. She has no history of hypertension, diabetes, or irregular eating habits, but practices weight reduction methods. She is not on any medications. Physical examination reveals a thin but well-nourished woman. Blood pressure is 100/68 mmHg with a pulse rate of 88 beats per minute (sitting) and 98/66 mmHg with a pulse rate of 102 beats per minute (standing). Except for trace edema, the rest of the examination is normal. Laboratory data:

Serum	Urine
Na^+ = 134 mEq/L	pH = 7.58
K^+ = 2.9 mEq/L	Na^+ = 40 mEq/L
Cl^- = 86 mEq/L	K^+ = 30 mEq/L
HCO_3^- = 36 mEq/L	Cl^- = 42 mEq/L
Creatinine = 1.1 mg/dL	
BUN = 32 mg/dL	
Glucose = 122 mg/dL	
Albumin = 4.2 g/dL	
ABG: pH = 7.48 pCO_2 = 48 mmHg HCO_3^- = 35 mEq/L	

Question 1 What is her acid–base disturbance?

Answer Since both pH and serum [HCO_3^-] are elevated, she has metabolic alkalosis as her primary acid–base disorder. The expected pCO_2 from respiratory compensation is 48 mmHg, which is in agreement with the reported pCO_2. Therefore, there is no additional acid–base disorder superimposed on metabolic alkalosis.

Question 2 Are urine electrolytes consistent with Cl^--resistant alkalosis?

Answer Yes. However, she has orthostatic pulse changes, suggestive of mild volume depletion. Therefore, she has Cl^--responsive alkalosis, and a drug use such as a diuretic should be suspected. Recent use of a thiazide or loop diuretic can cause urine electrolyte pattern, as shown in the table of laboratory results. If urine electrolytes are repeated 24 h later, Cl^- level will be low.

Case 5 A 42-year-old man presents to the ED with complaints of headache, weakness, fatigue, and shortness of breath. He has hypertension for 2 years. His medications include hydrochlorothiazide 25 mg QD, lisinopril 20 mg QD, metoprolol 50 mg BID, and KCl 40 mg QD. His blood pressure is 190/110 mmHg with a pulse of 74 beats per minute. There are no orthostatic changes. Pertinent physical examination reveals crackles in both lung fields and trace edema in lower extremities. Laboratory data:

Serum	Urine
Na^+ = 145 mEq/L	pH = 5.9
K^+ = 2.6 mEq/L	Na^+ = 100 mEq/L
Cl^- = 92 mEq/L	K^+ = 56 mEq/L
HCO_3^- = 34 mEq/L	Cl^- = 102 mEq/L
Creatinine = 1.1 mg/dL	
BUN = 10 mg/dL	
Glucose = 102 mg/dL	
Albumin = 4.0 g/dL	
ABG: pH = 7.52 pCO_2 = 40 mmHg HCO^{3-} = 33 mEq/L	

Question 1 What is his acid–base disturbance?

Answer Both the pH and serum [HCO_3^-] are elevated; therefore, he has metabolic alkalosis as his primary acid–base disorder. The expected pCO_2 from respiratory compensation is 47 mmHg, but the reported pCO_2 is 40 mmHg due to hyperventilation. Therefore, respiratory alkalosis is superimposed on metabolic alkalosis. Hyperventilation is due to shortness of breath.

Question 2 In addition to urine electrolytes, what other tests would you order to make the diagnosis?

Answer Plasma renin and aldosterone levels can help in the differential diagnosis of hypertension-associated metabolic alkalosis.

Twenty-four hours later, the results were available. Renin level was 0.01 (normal: 1–3 ng/mL/h) and aldosterone levels were 44 (range 5–20 ng/dL), suggesting primary aldosteronism as a cause of his metabolic alkalosis. After stabilization of the patient with furosemide and KCl supplementation, the patient was started on spironolactone 100 mg QD initially, and his BP improved. CT of the adrenal gland revealed a unilateral adenoma, which was surgically removed. His BP was subsequently controlled with diet.

Case 6 A 17-year-old man, a garbage collector for the city, is admitted for weakness, fatigue, dizziness, and occasional left knee pain. He craves Chinese food. He has no history of hypertension, and does not use illicit drugs, or alcohol. Blood pressure is 102/66 mmHg with a pulse rate of 88 beats per minute (sitting), and 88/60 mmHg with a pulse rate of 112 beats per minute (standing). Except for left knee tenderness, the rest of the examination is normal. Laboratory data:

Serum	Urine
Na^+ = 126 mEq/L	pH = 5.9
K^+ = 1.8 mEq/L	Na^+ = 180 mEq/L
Cl^- = 82 mEq/L	K^+ = 86 mEq/L
HCO_3^- = 36 mEq/L	Cl^- = 232 mEq/L
Creatinine = 0.7 mg/dL	Ca^{2+} = 0.008 mg/mg creatinine (normal: 0.06–1.0)
BUN = 20 mg/dL	24-h urine Ca^{2+} = 52 mg (range 150–200 mg)
Glucose = 90 mg/dL	FE_{Mg} = 2.8% (range 1.2–2.4%)
Ca^{2+} = 8.2 mg/dL	
Mg^{2+} = 0.8 mg/dL	
Albumin = 4.4 g/dL	
ABG: pH = 7.5 pCO_2 = 46 mmHg HCO^3 = 35 mEq/L	

Which one of the following options is the MOST likely diagnosis in this patient?

A. Bartter syndrome
B. Gitelman syndrome
C. Liddle syndrome
D. Diuretic abuse
E. Licorice ingestion

The answer is B. The patient's clinical manifestations and serum chemistry and ABG suggest either Bartter or Gitelman syndrome. However, five findings distinguish Gitelman syndrome from Bartter syndrome:

1. Hypomagnesemia
2. Hypocalciuria
3. Hypermagnesuria

4. Normal prostaglandin E_2 levels
5. Chondrocalcinosis (pseudogout)

In Bartter syndrome, urine Ca^{2+} and Mg^{2+} excretions are normal. Hyperprostaglandinemia E_2 is characteristic of Bartter syndrome. Also, pseudogout is absent in Bartter syndrome. Both syndromes are characterized by very high urine levels of Na^+ and Cl^-.

Liddle syndrome and licorice ingestion are associated with hypertension and volume expansion. Diuretic abuse can present with similar clinical findings, but the urine electrolyte levels do not suggest diuretic abuse. Also, mild hypercalcemia is seen in diuretic users. Elevation of uric acid and gouty attack can be observed with diuretic use; however, normocalcemia rules out the possibility of diuretic use. Thus, option B is correct.

Case 7 A 24-year-old man was referred to the renal clinic for evaluation of recent onset hypertension noted on a routine physical check-up. He has a strong family history of hypertension at an early age. He is not on any medications. Blood pressure is 190/104 mmHg with a pulse rate of 74 beats per minute. There are no orthostatic changes. His laboratory test results are consistent with hypokalemic metabolic alkalosis. He has high urine Cl^- relative to Na^+ and K^+, which are also high. His plasma renin and aldosterone levels are extremely low.

Question 1 Which one of the following is the most LIKELY diagnosis in this patient?

A. Primary aldosteronism
B. Renal artery stenosis
C. Liddle syndrome
D. Gitelman syndrome
E. Bartter syndrome

The answer is C. Primary aldosteronism and renal artery stenosis are associated with hypertension and high aldosterone levels. Patients with Gitelman and Bartter syndromes present with normal to low blood pressure. Renin and aldosterone levels are high rather than low in these syndromes. Therefore, the patient has Liddle syndrome, which is a genetic disorder due to mutations in ENaC. Renin and aldosterone levels are usually low, but normal values have also been reported. These low levels have been attributed to volume expansion and/or sclerosis of renin-producing cells in the juxtaglomerular apparatus.

Question 2 Which one of the following drugs is APPROPRIATE for this patient?

A. Spironolactone
B. Eplerenone
C. Hydrochlorothiazide
D. Metolazone
E. Amiloride

The answer is E. Patients with Liddle syndrome respond only to amiloride or triamterene and not to the other drugs mentioned above. In contrast, patients with primary aldosteronism respond to both spironolactone and amiloride. Thus, control of hypertension with spironolactone or eplerenone suggests the diagnosis of primary aldosteronism, whereas failure to control blood pressure suggests either Liddle syndrome or essential hypertension. Blood pressure improves with amiloride in Liddle syndrome, whereas it may not improve in essential hypertension. The latter requires probably more than one drug.

Case 8 Match the serum and urinary electrolyte pattern with patient history

	Serum $[Na^+]^a$	Serum $[K^+]$	Serum $[Cl^-]$	Serum $[HCO_3^-]$	Blood pH	Urine $[Na^+]$	Urine $[K^+]$	Urine $[Cl^-]$	Urine $[Ca^{2+}]^b$	Urine pH
A	136	3.0	89	28	7.48	100	40	15	200	7.2
B	135	2.8	86	32	7.50	40	30	15	150	5.8
C	136	3.0	86	32	7.51	80	44	60	250	6.1
D	137	2.9	84	30	7.48	120	80	60	50	6.2

[a]mEq/L, [b]mg/24-h

1. An 18-year-old man with craving for salty food and a mutation in Na/Cl cotransporter
2. A 12-year-old boy with a documented mutation in Na/K/2Cl cotransporter
3. A 27-year-old woman with vomiting for <2 days
4. A 40-year-old man with protracted vomiting for >7 days

Answers A = 3; B = 4; C = 2; D = 1.

The 18-year-old man carries the diagnosis of Gitelman syndrome, whereas the 12-year-old boy has Bartter syndrome. Clinically, both syndromes behave similarly. Level of urinary excretion of Ca^{2+} is the most important determinant of these syndromes. Hypocalciuria characterizes the Gitelman syndrome, whereas Ca^{2+} excretion is normal in Bartter syndrome (see Case 6). Laboratory data shown in D and C are consistent with Gitelman and Bartter syndromes, respectively.

From the above table, it is evident that early and late vomiting can be diagnosed based only on the urine electrolytes and urine pH. In early vomiting, the kidneys try to get rid of excess Na^+ and HCO_3^- in the urine to maintain near normal serum levels of these electrolytes. The urine pH is alkaline because of the presence of HCO_3^-. If this vomiting continues, the intravascular volume is depleted and metabolic alkalosis is sustained. This causes Na^+ and HCO_3^- reabsorption, resulting in low levels of these electrolytes and acidification of urine pH. During the correction phase of metabolic alkalosis, urine pH becomes alkaline because of HCO_3^- excretion. Thus,

laboratory data shown in A and B correspond to early and late vomiting, respectively.

Case 9 Match the following serum values with the clinical diagnoses

Case	Na^+	K^+	HCO_3^-	Renin	Aldosterone
A	↑	↓	↑	↓	↑
B	N/↑	↓	↑	↓	↑
C	↓	↓	↑	↑	↑

↑ increase, ↓ decrease, *N* normal

1. Primary aldosteronism
2. Glucocorticoid-remediable aldosteronism (GRA)
3. Renal artery stenosis

Answers A = 1; B = 2; C = 3.

Primary aldosteronism is the most common hypertensive disorder that is associated with low renin and high aldosterone levels. High levels of aldosterone are due to increased secretion of this hormone by either adrenal cortical adenoma or bilateral hyperplasia of the gland. Aldosterone promotes Na^+ reabsorption and K^+ secretion in the distal nephron. As a result, plasma volume is increased with an increase in serum [Na^+], and volume-dependent hypertension. Hypernatremia may also be caused by relative suppression of ADH due to volume expansion. Plasma renin level is low because of volume expansion. Primary aldosteronism is commonly seen in young patients with refractory hypertension, hypokalemia, hypernatremia, and saline-resistant metabolic alkalosis. Spironolactone or amiloride is the drug of choice for hypertension management. Laboratory data shown in A are consistent with primary aldosteronism.

Glucocorticoid-remediable hyperaldosteronism (GRA), also called familial hyperaldosteronism type 1, is caused by fusion of two enzymes: aldosterone synthase and 11β-hydroxylase. Some patients with GRA may have severe hypertension, hypokalemia, and metabolic alkalosis. Plasma renin is suppressed, but aldosterone levels are increased. Aldosterone secretion is stimulated by ACTH and not by angiotensin II. Therefore, administration of glucocorticoid suppresses excessive aldosterone secretion and improves hypertension. Laboratory data shown in B are consistent with GRA.

Patients with renal artery stenosis present with severe hypertension, hyponatremia, hypokalemia, and saline-resistant metabolic alkalosis. Hyponatremic hypertensive syndrome is characteristic of unilateral renal artery stenosis, but this syndrome has also been described in patients with bilateral renal artery stenosis. The pathophysiologic mechanism is that renal ischemia causes an increase in renin-AII-aldosterone, which in turn raises blood pressure. This increase in blood pres-

sure causes pressure natriuresis through the nonstenotic kidney, resulting in volume depletion and orthostatic hypotension. High levels of AII stimulate thirst and water consumption, finally leading to hyponatremia.

Hyponatremic hypertension can also be seen in patients with malignant hypertension, renin-secreting tumors, CKD, and those on diuretics. In young patients, renal artery stenosis is predominantly due to fibromuscular dysplasia, and in subjects aged >50 years, it is the atherosclerosis of the renal artery that causes hypertension. Laboratory data shown in C are consistent with renal artery stenosis.

Case 10 A 36-year-old woman was admitted for weakness, dizziness, and inability to walk for 2 weeks. She has a childhood history of hypothyroidism and sensorineural deafness. She denied vomiting. Her medications include synthroid for hypothyroidism and hydrochlorothiazide (HCTZ) for endolymph excess in the ear. Except for palpable goiter and low blood pressure, her physical examination is otherwise normal. Two months ago, her labs were normal. Current labs:

Serum	Urine
Na^+ = 134 mEq/L	pH = 6.0
K^+ = 2.6 mEq/L	Osmolality = 400 mOsm/kg H_2O
Cl^- = 84 mEq/L	Na^+ = 40 mEq/L
HCO_3^- = 36 mEq/L	K^+ = 50 mEq/L
Creatinine = 1.1 mg/dL	Cl^- = 20 mEq/L
BUN = 10 mg/dL	
Glucose = 90 mg/dL	
Albumin = 4.0 g/dL	
ABG: pH = 7.48 pCO_2 = 47 mmHg HCO_3^- = 35 mEq/L	

Which one of the following transport mechanisms is IMPLICATED for her childhood disease and metabolic alkalosis?

A. Na/H-ATPase
B. Na/K/2Cl cotransporter
C. Na/Cl cotransporter
D. Epithelial Na^+ channel (ENaC)
E. Cl/HCO_3 exchanger

The answer is E. This patient carries the diagnosis of Pendred syndrome, which is an autosomal recessive disorder. This disorder is characterized by sensorineural deafness and goiter due to defect in iodide organification. Pendred syndrome is caused by biallelic mutations in the solute carrier family 26A4 gene, which encodes pendrin. In the kidney, pendrin functions as a Cl/HCO_3 exchanger in the β-intercalated cell where Cl^- is reabsorbed and HCO_3^- is excreted into the lumen (Chap. 2). This

suggests that pendrin may protect against development of either salt loss or metabolic alkalosis under basal conditions because excess generation of HCO_3^- from any source is transported into the lumen and Cl^- is reabsorbed.

Under basal conditions, patients with Pendred syndrome do not develop any electrolyte or acid–base abnormalities. This suggests that there is a compensatory mechanism that prevents these abnormalities. Studies have shown that thiazide-sensitive Na/Cl cotransporter in the distal tubule takes over the function of pendrin as a Cl^- transporter. Conversely, when Na/Cl cotransporter is inhibited by a thiazide, pendrin expression and activity are increased. When both transporters are inhibited, volume depletion and metabolic alkalosis develop due to loss of NaCl in the urine. This happens when a Pendred syndrome patient is treated with a thiazide diuretic for endolymph accumulation in the ear. The mechanism by which this cross-talk between Na/Cl cotransporter and Cl/HCO_3 exchanger occurs is not completely understood.

Our patient with Pendred syndrome developed hypokalemia, hypochloremia, metabolic alkalosis, and volume depletion (low blood pressure) because of mutation in pendrin and inhibition of Na/Cl cotransporter by HCTZ. Discontinuation of HCTZ and hydration with normal saline and KCl would improve her electrolyte abnormalities and metabolic alkalosis. Thus, choice E is correct. Although pendrin interacts with other transporters, their deficiency or activation does not cause Pendred syndrome. Thus, choices A–D are incorrect.

Question 1 Which one of the following conditions of metabolic alkalosis does NOT respond to infusion of normal saline?

A. Vomiting
B. Nasogastric suction
C. Bartter syndrome
D. Gitelman syndrome
E. C and D

The answer is E. Both vomiting and nasogastric suction cause saline-responsive metabolic alkalosis, whereas Bartter syndrome and Gitelman syndrome are saline-resistant conditions of metabolic alkalosis. Thus, answer E is correct.

Suggested Reading

Galla JH. Metabolic alkalosis. J Am Soc Nephrol. 2000;11:369–75.
Gennari FJ. Metabolic alkalosis. In: Mount DB, Sayegh MH, Singh AJ, editors. Core concepts in the disorders of fluid, electrolytes and acid-base balance. New York: Springer; 2013. p. 275–96.
Gennari FJ. Pathophysiology of metabolic alkalosis: a new classification based on the centrality of stimulated collecting duct ion transport. Am J Kidney Dis. 2011;58:626–36.

Kandasamy N, Fugazola L, Evans M, et al. Life-threatening metabolic alkalosis in pendred syndrome. Eur J Endocrinol. 2011;165:167–70.
Laski ME, Sabatini S. Metabolic alkalosis, bedside and bench. Sem Nephrol. 2006;26:404–21.
Marston N, Kehl D, Copp J, et al. Alkalotics anonymous: severe metabolic alkalosis. Am J Med. 2014;127:25–7.
Palmer BF, Alpern RJ. Metabolic alkalosis. J Am Soc Nephrol. 1997;8:1462–9.
Reimann D, Gross P. Chronic, diagnosis-resistant hypokalaemia. Nephrol Dial Transplant. 1999;14:2957–61.
Soleimani M. The multiple roles of pendrin in the kidney. Nephrol Dial Transplant. 2015;30:1257–66.
Wall SM, Laza-Fernandez Y. The role of pendrin in renal physiology. Annu Rev Physiol. 2015;77:363–78.

Chapter 12
Respiratory Acidosis

Physiology

As stated in Chap. 4, respiratory acid–base disorders are due to changes in pCO_2. In normal individuals, the arterial partial pressure of carbon dioxide (pCO_2) is maintained at approximately 40 mmHg. This consistency of pCO_2 is maintained by the alveolar ventilation. Lungs are the only organs that eliminate (excrete) CO_2. Several physiologic mechanisms participate in the maintenance of CO_2 balance (given later). Disturbance in any one of these mechanisms leads either to retention (hypercapnia or an increase in pCO_2) or excessive elimination (hypocapnia or a decrease in pCO_2) of CO_2. The respiratory acid–base disorder that is associated with hypercapnia is called respiratory acidosis, whereas that associated with hypocapnia is known as respiratory alkalosis.

In a normal individual, CO_2 balance is maintained by the following mechanisms:

1. CO_2 production
2. CO_2 transport
3. CO_2 elimination
4. Control of ventilation by central nervous system (CNS)

CO_2 Production

- CO_2 is produced by metabolism of carbohydrates and fats.
- Approximately 15000 mmol of CO_2 are produced daily.
- Heavy exercise generates severalfold higher quantity of CO_2 than when the body is in resting state.
- Lungs are the only organs that excrete all the CO_2 that is produced.
- Thus, the arterial pCO_2 tension represents the balance between its production and elimination. The inspired CO_2 is negligible.

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_12

CO_2 Transport

- The CO_2 that is produced during metabolism is transported by the blood (plasma and red blood cells) to the lungs via pulmonary arteries.
- The pCO_2 difference (gradient) between the tissues and alveoli is only 6 mmHg.
- In red blood cells, CO_2 is converted to carbonic acid (H_2CO_3) in the presence of carbonic anhydrase.
- H_2CO_3 then dissociates into H^+ and HCO_3^-. It is this HCO_3^- that diffuses into the plasma via Cl/HCO_3 exchanger and is carried to the lungs, where it is converted back to CO_2.

CO_2 Elimination

- Alveolar ventilation is the major determinant of CO_2 elimination.
- A decrease in alveolar ventilation causes retention of CO_2, resulting in an increase in total body CO_2 balance.
- Other determinants include blood flow through the aerated lung, diffusion of CO_2 from the capillary to the alveolar space, and physiologic dead space.

CNS Control of Ventilation

In a normal individual, variations in pCO_2, partial pressure of oxygen (pO_2), and pH are minimized and kept within normal limits by the respiratory control system, which includes the following:

1. Sensors (chemoreceptors)
2. Central controller (medulla and pons)
3. Effectors (respiratory muscles)

Sensors

Two types of chemoreceptors are involved in ventilation:

1. Central chemoreceptors, located in the medulla, are surrounded by the interstitial and cerebrospinal fluid and respond to changes in $[H^+]$ or pCO_2. For example, an increase in $[H^+]$, i.e., a decrease in pH, stimulates respiration and decreases pCO_2. These responses, in turn, raise pH. On the other hand, a decrease in $[H^+]$ or an increase in pH depresses alveolar ventilation and causes retention of pCO_2, so that the pH is returned to near normal. An increase in pCO_2 stimulates ventilation, whereas a decrease depresses ventilation. Central chemoreceptors are not sensitive to changes in pO_2

2. Peripheral chemoreceptors are located in the carotid body and aortic arch. They respond to decreases in pO_2 and pH and increases in pCO_2. The sensitivity to changes in pO_2 begins at around 500 mmHg, but little response occurs until pO_2 is <60 mmHg. The receptors of carotid body are more sensitive to decrease in pO_2 (hypoxemia) than the receptors located in the aortic arch

Medullary Center

1. Central controller includes neurons located in the medulla and pons, which are referred to as respiratory centers
2. Medullary respiratory center has two identifiable areas of neurons. One group of neurons is located in the dorsal region of the medulla (nucleus tractus solitarius). It is called the dorsal respiratory group, which is involved in inspiration (firing on inspiration). In addition, these neurons receive afferent stimuli from peripheral and central chemoreceptors and from receptors in the lung. The other group of neurons, the ventral respiratory group, controls both expiration (firing on expiration) and inspiration

Effectors

1. Once changes are sensed in the medullary respiratory center, they are transmitted through nerves to the muscles of respiration (diaphragm, intercostal muscles, abdominal muscles, and sternocleidomastoid muscles). It is the coordinated effort of these muscles that is responsible for ventilation

Any disturbance in sensing and signaling results in either hypercapnia or hypocapnia, leading to either respiratory acidosis or respiratory alkalosis, respectively. Let us discuss respiratory acidosis.

Respiratory Acidosis

Respiratory acidosis, also called primary hypercapnia, is initiated by an increase in arterial pCO_2. This increase is related to decreased excretion relative to the production of CO_2. Whenever pCO_2 increases, the pH falls. The excess H^+ is immediately (within minutes) buffered by nonbicarbonate buffers, such as hemoglobin, phosphates, and plasma proteins, so that HCO_3^- is not used up. During this buffering, some HCO_3^- is also formed from dissociation of H_2CO_3. The acute nonbicarbonate buffer response is completed within 10–15 min, and a steady state condition persists for 1 h. If hypercapnia continues for >12 h, the kidneys generate additional HCO_3^- by excretion of H^+, and the maximum level of HCO_3^- generation is completed within 3–5 days. Thus, respiratory acidosis can be classified into acute (<12 h) or chronic (>5 days) types. Both acute and chronic hypercapnias are associated with hypoxemia.

Pathophysiology

From the above discussion, respiratory acidosis can develop from any or combination of the following ventilation abnormalities: (1) overproduction of CO_2; (2) decreased alveolar ventilation; (3) impaired gas exchange; (4) decreased respiratory center response; and (5) abnormalities of the chest wall and respiratory muscles.

Overproduction of CO_2 Either an increase or decrease in CO_2 production can occur in several clinical settings, as shown in Table 12.1. This excess CO_2 production is eliminated by proportionate increase in alveolar ventilation. Thus, positive CO_2 balance does not usually develop with intact respiratory system. Therefore, overproduction of CO_2 does not cause significant hypercapnia. However, CO_2 retention does occur whenever there is an abnormality in alveolar ventilation.

Decreased Alveolar Ventilation (Hypoventilation) Alveolar ventilation (V_A) is defined as the amount of gas that reaches the alveoli per minute. Decreased alveolar ventilation may be related to low minute ventilation (V_E, which is equal to the tidal volume and respiratory rate) or an increase in dead space ($V_{D,}$ which is an airway volume that does not participate in gas exchange) or both. Tidal volume (V_T) is the amount of gas inspired or expired per breath. V_E (minute ventilation) refers to total ventilation, which is expressed as L/min; however, all this volume does not participate in gas exchange. V_A (alveolar ventilation) refers to that volume of air in the alveoli participating in gas exchange. Therefore, V_A is equal to:

$$V_A = \left(V_T - V_D\right) \times \text{Respiratory rate}$$

or

$$V_A = \left(V_E - V_D\right)$$

Alveolar hypoventilation causes not only CO_2 retention but also inadequate (poor) oxygenation. Impaired response of medullary CO_2 receptors (due to narcotics) or carotid pO_2 receptors (due to trauma or surgical removal) may cause alveolar hypoventilation.

Table 12.1 Clinical settings associated with CO_2 production

Increase	Decrease
Fever	Hypothermia
High glucose loads	High fat loads
Exercise	Inactivity (sleep)
Hyperthermia	Hypothyroidism
Hyperthyroidism	Weight loss
Multiorgan failure	Decreased work of breathing (mechanical ventilation, sedatives)
Increased work of breathing (severe dyspnea)	

Increase in V_D (dead space) alone rarely causes alveolar hypoventilation unless the ratio of V_D/V_T (dead space to tidal volume) exceeds 0.6. Normal V_D/V_T ratio is 0.3. Conditions such as pulmonary embolism and shock lung may increase V_D and result in high ratio. Also, relative decrease in V_T can be seen in patients with increased respiratory rate (rapid but shallow breathing) due to neuromuscular disease and pulmonary edema or fibrosis. Increased V_D/V_T ratio is thought be the mechanism for acute exacerbation of COPD due to rapid shallow breathing. Thus, V_D is an important contributor of alveolar hypoventilation.

Impaired Gas Exchange Impaired alveolar gas exchange (ventilation–perfusion mismatch) can lead to hypoxemia and hypercapnia. Patients with lung disease and superimposed acute conditions such as pulmonary edema and pneumonia can cause impaired gas exchange with resultant hypoxemia and hypercapnia.

Decreased Respiratory Center Response Drugs such as sedatives and narcotics, CNS diseases such as medullary infarcts and tumors, and diseases like hypothyroidism cause hypercapnia by inhibiting the central respiratory drive. Sedatives and narcotics should be used with caution in patients with severe asthma or COPD who retain CO_2. However, some individuals with anxiety or pain who develop hypocapnia because of hyperventilation may benefit from the use of these drugs by lowering pH.

Abnormalities of the Chest Wall and Respiratory Muscles Hypercapnia develops despite normal central drive and lung structure. Disorders of respiratory muscles and motor neurons are examples of this pathophysiologic mechanism of hypercapnia. Fatigue and weakness of diaphragm is an important contributor for hypercapnia. Electrolyte abnormalities such as severe hypokalemia and hypophosphatemia and malnutrition may cause respiratory muscle weakness and cause CO_2 retention. Chest wall stiffness such as kyphoscoliosis is another cause for hypercapnia.

Secondary Physiologic Response to Hypercapnia

As stated earlier, the renal and extrarenal mechanisms respond to an increase in pCO_2 by preventing loss of HCO_3^- so that dangerous decreases in pH are avoided. Although acute respiratory acidosis causes low pH, chronic respiratory acidosis maintains pH at slightly low but near-normal levels because of renal regeneration of HCO_3^-. The secondary responses to both acute and chronic respiratory acidosis are given below:

Acute respiratory acidosis: For each mmHg increase in pCO_2, HCO_3^- increases by 0.1 mEq/L.

Chronic respiratory acidosis: For each mmHg increase in pCO_2, HCO_3^- increases by 0.4 mEq/L.

Table 12.2 shows the relationship between rise in pCO_2, secondary response (compensation), and arterial pH in acute and chronic respiratory acidosis.

Table 12.2 Relationship between hypercapnia, secondary response, and pH

Type	pCO_2 (mmHg)	Expected secondary response (compensation)	Expected serum $[HCO_3^-]$	pH (calculated from Henderson equation) after compensation
Normal	40	–	24	7.40
Acute	70[a]	For each mmHg increase in pCO_2, HCO_3^- increases by 0.1 mEq/L, $\Delta pCO_2 = 30$ (70–40 = 30 × 0.1 = 3)	27 (24 + 3 = 27)	7.18
Chronic	70[a]	For each mmHg increase in pCO_2, HCO_3^- increases by 0.4 mEq/L, $\Delta pCO_2 = 30$ (70–40 = 30 × 0.4 = 12)	36 (24 + 12 = 36)	7.34

[a]Arbitrary value

Mechanism of Secondary Physiologic Response

Acute Respiratory Acidosis An increase in pCO_2 increases the production of carbonic acid (H_2CO_3) and H^+ production. As a result of increased H^+, the blood pH decreases (as shown in Table 12.2). The secondary physiologic response for this low pH or hypercapnia is an increase in plasma HCO_3^- concentration, which is due to buffering of H^+ by nonbicarbonate buffers such as red blood cells, hemoglobin, and tissue buffers. The increase in HCO_3^- concentration is 0.1 mEq/L for each 1 mmHg increase in pCO_2 above 40 mmHg (as shown in Table 12.2). The adaptive increase in HCO_3^- concentration is complete in 10–15 min. Following this period of time, no further changes in HCO_3- occur for hours, and this period is called *acute steady state*.

Chronic Respiratory Acidosis As stated above, the kidney responds to chronic hypercapnia by increasing serum HCO_3^- concentration. This occurs by increasing excretion of H^+ mostly in the form of NH_4^+ (see Chap. 2). These changes start to happen 12–24 h after hypercapnia. Excretion of H^+ results in formation and reabsorption of HCO_3^-. This increase in HCO_3^- is complete in 3–5 days. As shown in Table 12.2, for each mmHg increase in pCO_2, HCO_3^- increases by 0.4 mEq/L. Secretion of H^+ and reabsorption of HCO_3^- seem to occur in the proximal and distal tubules. Studies have shown an increased activity of luminal Na/H exchanger and basolateral Na/HCO_3 cotransporter in the proximal tubule. Also, chronic hypercapnia has been shown to induce luminal insertion of H-ATPase in the proximal tubule and in type A intercalated cells of the cortical and medullary collecting ducts as well as abundance of basolateral Cl/HCO_3 exchanger in the latter type of cells. These studies provide evidence for increased luminal H^+ secretion and increased basolateral HCO_3^- reabsorption in chronic hypercapnia. With the increase in serum HCO_3^- concentration, a new steady develops, but the blood pH will not return to normal. Therefore, the patient will have persistent acidic pH despite high concentration of HCO_3^-.

The increased HCO_3^- reabsorption is associated with inhibition of Cl^- reabsorption. As a result, Cl^- is excreted in the urine with depletion of body stores. Cl^- is also excreted with Na^+ and K^+. Thus, persistent hypochloremia exists in chronic respiratory acidosis.

Acute Respiratory Acidosis

Causes

There are several causes of acute respiratory acidosis, as shown in Table 12.3.

Table 12.3 Causes of acute respiratory acidosis

Depression of medullary respiratory center
Drugs, anesthetics, sedatives, opiates
Cerebral trauma or infarct
Central sleep apnea
Cardiac arrest
Failure of motor functions of respiratory muscles and chest wall
Drugs: succinylcholine, curare, aminoglycosides, fluoroquinolones
High cervical cordotomy
Myasthenia gravis crisis
Guillain–Barrè syndrome
Status epilepticus
Tetanus
Acute botulism poisoning
Familial hypokalemic periodic paralysis
Severe hypophosphatemia
Airway obstruction
Aspiration
Laryngospasm
Severe bronchospasm
Obstructive sleep apnea
Ventilatory defects
Flail chest
Pneumothorax
Hydrothorax
Adult respiratory distress syndrome
Acute pulmonary embolism
Acute pulmonary edema
Severe asthma
Severe pneumonia
Mechanical ventilation, increased production of CO_2 due to high carbohydrate feedings and fixed minute ventilation

Selected Conditions of Acute Respiratory Acidosis

Opiates Opioid drugs such as morphine and related agents activate μ-opiate receptors and induce respiratory depression. These receptors are widespread in the ventrolateral medulla, and their activation reduces breathing and tidal volume as well as respiratory response to hypercapnia or hypoxemia. The result is the development of acute respiratory acidosis. Respiratory depression is prolonged in patients with renal and liver failure. Drug overdose and severe hypercapnia require mechanical ventilation. Opiate antagonists such as naloxone (Narcan) improve hypercapnia by competitively inhibiting μ-opiate receptors. Management of sleep-disordered breathing by positive pressure ventilation is also recommended. Life-threatening acidosis requires bicarbonate therapy.

Overdose of barbiturates also causes respiratory depression with resultant hypercapnia and respiratory acidosis.

Acute Severe Asthma In general, patients with asthma develop respiratory alkalosis and also metabolic acidosis due to lactic acid production. However, acute respiratory acidosis is rather uncommon and occurs in 10% of patients. It develops only when airway obstruction is extremely severe due to mucus plugging and FEV_1 falls below 20% of its predicted value, or peak expiratory flow rate <100 L/min.

Clinically, patients with acute respiratory acidosis present with stupor or coma, tachypnea, tachycardia, hypertension, and pulsus paradoxus. Use of accessory muscles of respiration is quite common. A normal pCO_2 in a patient with acute asthma is suggestive of impending respiratory failure, requiring intubation. Bronchodilators, steroids, and ventilatory management to improve hypercapnia and hypoxemia are necessary.

Increased CO_2 Production High carbohydrate diet or solutions containing high glucose generate excess CO_2. In a healthy individual, excess production of CO_2 stimulates alveolar ventilation, and CO_2 is eliminated. In malnourished individuals, patients with lung disease, and patients on ventilators with fixed ventilation, the excess production of CO_2 by carbohydrate intake is not eliminated. As a result, these patients develop hypercapnia and acute respiratory acidosis. A decrease in carbohydrate load improves respiratory acidosis.

Other conditions that increase CO_2 production include exercise, sepsis, hyperthermia, burns, and multiorgan failure. Regarding hyperthermia, CO_2 production increases by 13% for each 1 °C increase in temperature above normal.

Acute Respiratory Acidosis Superimposed on Chronic Respiratory Acidosis This condition usually occurs in patients with limited alveolar ventilation such as chronic obstructive pulmonary disease. Mucus plugging, inflammation, bronchospasm, and respiratory muscle fatigue may contribute to hypercapnia. The basic approach to management is maintenance of adequate oxygenation by low-flow controlled oxygen supplementation, with relatively infrequent use of intubation and controlled ventilation.

Neuromuscular Disorders A variety of motor neuron disorders such as myasthenia gravis and amyotrophic lateral sclerosis cause skeletal muscle and diaphragmatic

weakness, leading to hypoventilation and hypercapnia. Demyelinating diseases such as multiple sclerosis and Guillain-Barrė syndrome also cause hypercapnia. Noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation can maintain adequate ventilation during acute exacerbation or in severe disease.

Antibiotics The most common antibiotics that cause neuromuscular blockade are aminoglycosides. These drugs are rather contraindicated in myasthenia gravis patients. Other drugs such as fluoroquinolones and colistin have also been implicated in causing hypercapnia.

Clinical Manifestations

As stated earlier, acute respiratory acidosis causes hypoxemia, resulting in several organ dysfunctions.

CNS manifestations predominate and include the following:

1. Signs and symptoms: Nausea, vomiting, restlessness, headache, confusion, seizures, and coma
2. Cerebral blood flow: Increases acutely due to cerebral vasodilation of capillaries and venules. This cerebral vasodilation is mediated by nitric oxide
3. Intracranial pressure: Hypercapnia increases intracranial pressure due to increased blood volume and increased vascular pressure caused by vasodilation

Cardiac manifestations include an increase in blood pressure and heart rate secondary to increased sympathetic tone. Cardiac output increases. Also, coronary blood flow increases due to hypercapnia-induced vasodilation. Both peripheral vasodilation (due to hypercapnia) and vasoconstriction (due to increased sympathetic tone) occur in patients with acute respiratory acidosis. Arrhythmias are also common.

Renal effects include renal vasodilation with mild hypercapnia and vasoconstriction at pCO_2 >70 mmHg. Renin–angiotensin II (AII)–aldosterone axis is stimulated by hypercapnia-induced sympathetic tone. Antidiuretic hormone (ADH) secretion is also increased.

Other effects include skeletal muscle contraction, particularly diaphragmatic movement is reduced.

Also, acute and chronic hypercapnias increase the production of gastric acid.

Diagnosis

- History of cough, shortness of breath, fever, asthma, congestive heart failure, or trauma to head or back, drug use, and other medical conditions should be obtained.
- Physical examination should include vital signs, breathing pattern, body habitus, teeth (dentures, if any), mouth for any foreign material, chest exam for shape and

accessory muscle use, auscultation of lungs for crackles, wheezing, tactile fremitus, movement of diaphragm, cardiac examination for an S_3 and an S_4, abdomen for muscle use, lower extremities for edema, upper extremities for clubbing, and a good neurologic examination.

- Laboratory results:
  1. Arterial blood gas (ABG): low pH (<7.25), slightly elevated serum HCO_3^- (<30 mEq/L), and elevated pCO_2 (>60 mmHg) characterize acute respiratory acidosis; pH, expected [HCO_3^-], and pCO_2 shown in Table 12.2 distinguish acute respiratory acidosis from chronic respiratory acidosis
  2. Serum chemistry, including Ca^{2+}, Mg^{2+}, phosphate, and hemoglobin
  3. A slight increase in serum Na^+ (2–4 mEq/L) is observed
  4. A slight increase in serum K^+ (~0.1 mEq/L for 0.1 unit decrease in pH) is common
  5. A slight decrease in serum Cl^- is seen because of Cl^- entry into red blood cells in exchange for HCO_3^- (chloride shift)
  6. Hyperphosphatemia is common due to release of phosphate from tissues (not present in chronic respiratory acidosis)
  7. Ca^{2+} and Mg^{2+} are usually normal, but slight increases have been reported
  8. Normal anion gap
  9. Acidic urine pH (<5.5)
  10. Chest x-ray and electrocardiogram (EKG)
  11. Calculation of alveolar–arterial (A–a) gradient for gas exchange

Treatment

Correction of the underlying cause should be attempted whenever possible.

Immediate treatment should include the following:

1. Establishing a secure patent airway in both awake and obtunded patients
2. Hypercapnic encephalopathy may occur in patients with narcotic overdose and in those with chronic hypercapnia and superimposed acute respiratory acidosis
3. Administration of O_2 to improve hypoxemia. This is more important than lowering pCO_2 and raising pH. Assisted ventilation should be initiated promptly in severely obtunded, comatosed patients, or patients with pH <7.10. If a patient is awake and hemodynamically stable, O_2 by nasal cannula or by high-flow Venturi face mask may be sufficient. The aim of O_2 therapy is to achieve pO_2 of 60–70 mmHg or an O_2 saturation >88%
4. Mechanical ventilation is indicated in apneic, obtunded, and hemodynamically unstable patients with pH <7.10 and pCO_2 >80 mmHg. Lowering pCO_2 may be sufficient to raise pH, but $NaHCO_3$ or THAM is needed in some patients
5. Loop diuretics may be needed in a patient with crackles
6. Antibiotics, β_2-agonists, and other bronchodilators, as well as corticosteroids, may be necessary in patients with infection and wheezing, to improve ventilation

7. As mentioned previously, carbohydrate feedings in ventilator-dependent patients should be minimized to prevent excess CO_2 generation. Calories from fat emulsions should be encouraged

Remember that clinical assessment and proper use of pharmacotherapy are extremely important in the management of acute respiratory acidosis.

Chronic Respiratory Acidosis

Steady-state hypercapnia is achieved in 3–5 days following secondary renal adaptive changes that increase serum [HCO_3^-] by 0.4 mEq/L for each mmHg increase in pCO_2 above the normal level. Thus, the acid–base pattern of chronic acidosis is different from that of acute acidosis.

Causes

Table 12.4 shows various causes of chronic respiratory acidosis.

Table 12.4 Causes of chronic respiratory acidosis

Depression of medullary respiratory center
Chronic sedative and opiate addiction
Brain tumors
Primary alveolar hypoventilation
Obesity–hypoventilation syndrome
Bulbar poliomyelitis
Failure of motor functions of respiratory muscles and chest wall
Spinal cord injury
Multiple sclerosis
Muscular dystrophy
Amyotrophic lateral sclerosis
Myxedema
Poliomyelitis
Diaphragmatic paralysis
Airway obstruction
Chronic obstructive pulmonary disease (COPD) (most common cause)
Ventilatory defects
Hydrothorax
Fibrothorax
Kyphoscoliosis
Interstitial lung fibrosis
Severe chronic pneumonia
Extreme obesity

Selected Conditions of Chronic Respiratory Acidosis

Primary Alveolar Hypoventilation Syndrome (PAHS) This syndrome is a rare syndrome, which is characterized by hypercapnia and hypoxemia in the absence of pulmonary, CNS and neuromuscular disorders. PAHS is related to abnormal chemoreceptor function. Traditionally, this syndrome is called Ondine's curse and occurs in children and young adults. Full discussion of this syndrome is beyond the scope of this book. Treatment consists of noninvasive positive pressure ventilation in milder cases to mechanical ventilation in most severe cases. New treatments that are being evaluated include diaphragmatic pacing and the use of progestin desogestrel.

Obesity-Hypoventilation Syndrome (OHS) This syndrome is seen in obese subjects without chronic lung disease. OHS is characterized by an elevation in pCO_2 >45 mmHg when the subject is awake. During sleep, more significant hypoventilation with impaired gas exchange is observed. Many patients with OHS have associated obstructive sleep apnea syndrome, making OHS as a heterogeneous disorder. The major problem in OHS is decreased responsiveness of the respiratory medullary center to hypercapnia. Leptin is thought to increase ventilation by stimulating the respiratory medullary center. Consequently, leptin's deficiency or its decreased responsiveness is implicated in the pathophysiology of OHS.

Treatment with the use of either bilevel positive airway pressure (BPAP) or continuous positive airway pressure (CPAP) has proven effective in OHS. If hypoxia does not improve with either of the above modalities, use of nocturnal O_2 may be helpful. Concomitant treatment for weight loss is helpful not only respiratory but other systemic complications associated with OHS.

Chronic Obstructive Pulmonary Disease (COPD) Hypercapnia in COPD carries poor prognosis. Irreversible airway obstruction causes air trapping, leading to poor gas exchange and hypoventilation. Hypoxemia, airway obstruction, and alveolar loss are some of the poor prognostic factors. Patients with COPD have decreased chemical responsiveness to hypercapnia and hypoxemia. Bronchodilators (short- and long-acting), inhaled corticosteroids, oxygen for hypoxemia, and noninvasive positive pressure ventilation (NIPPV) are commonly used for chronic and acute management of COPD. NIPPV treatment was found to be associated with few intubations, hospitalizations, and improve all-cause morbidity as compared with usual care.

Clinical Manifestations

- Less severe compared to patients with acute respiratory acidosis because of near-normal pH.
- Hypoxemia and associated symptoms are common.

- CNS manifestations include tremors, ataxia, and poor appetite. Cerebral vasodilation and blood flow are increased but not to the extent of acute hypercapnia.
- Cardiovascular effects are pulmonary hypertension (cor pulmonale), peripheral edema, and supraventricular as well as ventricular arrhythmias. Cardiac output is normal or near normal.
- Glomerular filtration rate (GFR) is normal.
- Bone disease is present but less severe compared with metabolic acidosis. Hypercalciuria is less common or absent.

Diagnosis

- As in acute respiratory acidosis, history and physical findings are important in chronic respiratory acidosis. Body habitus, deformed chest, and clubbing are prominent findings.
- Laboratory results:

1. ABG: pH near normal (>7.30), elevated HCO_3^- (>32 mmHg), and elevated pCO_2 (>60 mmHg) usually characterize chronic respiratory acidosis
2. Serum Na^+ is slightly elevated
3. K^+ is normal
4. Cl^- decreases proportionately with the increase in HCO_3^-
5. Ca^{2+} and Mg^{2+} are normal
6. When K^+ is low, suspect superimposed metabolic alkalosis or excessive β_2-agonist therapy
7. AG is normal, when high, suspect superimposed metabolic acidosis such as lactic acidosis
8. Urine pH is <5.5
9. Secondary polycythemia is common
10. Chest x-ray if infection is suspected and for evaluation of chronic pneumonia

Treatment

- Treatment of chronic respiratory acidosis is different from that of acute respiratory acidosis.
- Address the cause of chronic respiratory acidosis and treat appropriately.
- The primary goal of treatment is to maintain adequate oxygenation as well as alveolar ventilation and amelioration of hypoxemia.
- In contrast to acute respiratory acidosis, excessive oxygenation should be avoided in order to prevent CNS depression.
- Avoid long-term sedatives and sleeping pills because they depress CNS drive.

- Do not treat the acidic pH; however, patients with cor pulmonale and lower extremity edema receive diuretics, and their pH may be slightly elevated.
- Antibiotics for infections are indicated.
- Bronchodilator therapy should be continued.
- Weight reduction methods should be suggested for obese individuals.
- Dietary modification is needed to reduce CO_2 production.
- If severe hypoxemia (arterial $pO_2 < 50$ mmHg) persists, continuous low-flow O_2 therapy may improve pulmonary circulation and gas exchange through reduction in pulmonary vasoconstriction.
- The goal of O_2 therapy is to maintain pO_2 between 60 and 70 mmHg and O_2 saturation of 88–93%.
- Mechanical ventilation is not necessary for a patient who is alert and able to cough and follow medical therapy.
- Obtunded patients and patients with superimposed acute respiratory acidosis may require mechanical ventilation. Minute ventilation should be raised to achieve baseline pH and pCO_2. Sudden drop in pCO_2 may induce posthypercapnic metabolic alkalosis.

Study Questions

Case 1 A 65-year-old man with a history of chronic obstructive pulmonary disease (COPD) is admitted for evaluation of shortness of breath. On admission, his laboratory values are as follows:

Serum	ABG
$Na^+ = 134$ mEq/L	pH = 7.35
$K^+ = 3.6$ mEq/L	$pCO_2 = 64$ mmHg
$Cl^- = 90$ mEq/L	$pO_2 = 70$ mmHg
$HCO_3^- = 34$ mEq/L	$HCO_3^- = 33$ mEq/L
Creatinine = 1.1 mg/dL	
BUN = 12 mg/dL	
Glucose = 100 mg/dL	

Question 1 Characterize the acid–base disorder.

Answer Follow step-by-step approach given in Chap. 4 to analyze this acid–base disorder.

Step 1 According to the Henderson equation, the $[H^+]$ is 45 nmol/L and corresponds to a pH of 7.35.

Step 2 On the basis of low pH and elevated pCO_2 and HCO_3^-, the primary acid–base disturbance is respiratory acidosis.

Step 3 The AG is 10, which is normal.

Step 4 The cause for this patient's respiratory acidosis is COPD.

Step 5 The compensation for respiratory acidosis is renal reabsorption of HCO_3^-. Gathering from Table 12.2, the patient has a primary chronic rather than an acute respiratory acidosis.

Step 6 The immediate treatment is administration of low-flow O_2 by nasal cannula and subsequent correction of the precipitating factor.

Case 2 A college-going, healthy student is brought to the Emergency Department (ED) in obtunded condition by his friends 24 h after a birthday party. He has a low respiratory rate, requiring elective intubation. His blood pressure is 120/78 mmHg with a pulse rate of 86 beats per minute. Serum chemistry is normal except for HCO_3^- of 27 mEq/L. AG is normal. ABG prior to intubation: pH 7.09, pCO_2 70 mmHg, pO_2 88 mmHg, and HCO_3^- 26 mEq/L.

Question 1 Characterize the acid–base disorder.

Answer On the basis of low pH and high pCO_2 and HCO_3^-, the acid–base disturbance is an uncomplicated respiratory acidosis.

Question 2 Is it acute or chronic respiratory acidosis?

Answer It is acute respiratory acidosis, as the expected HCO_3^- is 27 mEq/L. In acute respiratory acidosis, HCO_3^- increases by 0.1 mEq/L for each mmHg increase in pCO_2.

Thus, the excess pCO_2 is 30 mmHg (70 − 40 = 30), which elevates serum HCO_3^- to 27 mEq/L.

Question 3 Why is his respiratory rate decreased?

Answer On the basis of his history of attending a birthday party, one can assume that he may have taken a drug that depressed the respiratory center. Urine toxicology showed the presence of opiates.

Case 3 A 42-year-old man with a history of kyphoscoliosis and right heart failure is admitted for progressive shortness of breath and worsening peripheral edema. He is on furosemide for heart failure. Blood pressure is 140/82 mmHg and a pulse rate

is 88 beats per minute. Respiratory rate is 18 per minute. Pertinent findings are distant breath sounds bilaterally and 1+ pitting edema in lower extremities. Laboratory results:

Serum	ABG
Na^+ = 137 mEq/L	pH = 7.34
K^+ = 4.2 mEq/L	pCO_2 = 68 mmHg
Cl^- = 91 mEq/L	pO_2 = 52 mmHg
HCO_3^- = 35 mEq/L	HCO_3^- = 34 mEq/L
Creatinine = 0.9 mg/dL	
BUN = 14 mg/dL	
Glucose = 90 mg/dL	
Albumin = 4.5 g/dL	

Question 1 What is the acid–base disturbance?

Answer The increases in both HCO_3^- and pCO_2 with relatively low pH indicate that the acid–base disorder is respiratory acidosis.

Question 2 Is it a mixed acid–base disorder?

Answer No. On the basis of the renal response to hypercapnia, the expected HCO_3^- should be 35 ($68 - 40 = 28 \times 0.4 = 11.2$), which coincides with the reported HCO_3^- of 35 mEq/L. Therefore, the acid–base disorder is chronic respiratory acidosis. Also, low Cl^- is consistent with chronic respiratory acidosis. The AG is 11, suggesting that no other metabolic acid–base disorder is present.

One month later, the patient comes back with cough and yellowish sputum production. Chest x-ray shows bilateral infiltrates. He is confused and lethargic. Laboratory results:

Serum	ABG
Na^+ = 140 mEq/L	pH = 7.28
K^+ = 3.5 mEq/L	pCO_2 = 88 mmHg
Cl^- = 100 mEq/L	pO_2 = 48 mmHg
HCO_3^- = 34 mEq/L	HCO_3^- = 32 mEq/L
Creatinine = 0.9 mg/dL	
BUN = 12 mg/dL	
Glucose = 84 mg/dL	
Albumin = 4.5 g/dL	

Question 3 Characterize the acid–base disorder.

Answer Compared with previous laboratory results, the current laboratory results show an increase in pCO_2, a decrease in pH, and worsening hypoxemia. This patient has acute respiratory acidosis superimposed on chronic respiratory acidosis.

Question 4 Does this patient need $NaHCO_3$ administration to improve pH?

Answer No. The patient requires intubation and an increase in minute ventilation. Lowering of pCO_2 to 66 mmHg raises his pH from 7.28 to 7.34, assuming no change in serum [HCO_3^-]. Actually, administration of $NaHCO_3$ increases pCO_2 and worsens pH.

Case 4 A 64-year-old woman with COPD develops diarrhea of 1 week duration. She says that she took enough fluids "to keep up with diarrhea," but abdominal cramps and slight dizziness brought her to the ED. She is alert and oriented. Her blood pressure is 120/60 mmHg with a hear rate of 96 per minute. Respiratory rate is 19 per minute. She has orthostatic blood pressure and pulse changes. Laboratory results:

Serum	ABG
Na^+ = 136 mEq/L	pH = 7.27
K^+ = 3.2 mEq/L	pCO_2 = 62 mmHg
Cl^- = 100 mEq/L	pO_2 = 88 mmHg
HCO_3^- = 28 mEq/L	HCO_3^- = 27 mEq/L
Creatinine = 1.0 mg/dL	
BUN = 24 mg/dL	
Glucose = 92 mg/dL	

Question 1 What is the acid–base disturbance?

Answer Low pH and high pCO_2 and HCO_3^- indicate that the primary acid–base disorder is chronic respiratory acidosis. If she had acute respiratory acidosis, her serum HCO_3^- would have been 26 (24 + 2) rather than 28 mEq/L.

The pH and serum [HCO_3^-] are low for chronic respiratory acidosis. Since she has diarrhea, she developed non-AG metabolic acidosis, which lowered HCO_3^- and pH. Note that pCO_2 may have been slightly lowered because of mild increase in respiratory rate. Thus, the patient has chronic respiratory acidosis and non-AG metabolic acidosis.

Case 5 A 56-year-old man with a history of COPD and essential hypertension is admitted for recently exacerbated shortness of breath and fatigue. He is on bronchodilators and hydrochlorothiazide (HCTZ). Laboratory results:

Serum	ABG
Na^+ = 134 mEq/L	pH = 7.42
K^+ = 3.6 mEq/L	pCO_2 = 59 mmHg
Cl^- = 91 mEq/L	pO_2 = 62 mmHg
HCO_3^- = 37 mEq/L	HCO_3^- = 36 mEq/L
Creatinine = 0.9 mg/dL	
BUN = 14 mg/dL	
Glucose = 90 mg/dL	
Albumin = 4.5 g/dL	

Question 1 What is the acid–base disturbance?

Answer The increase in HCO_3^- and pCO_2 with slightly elevated pH indicates that the acid–base disorder is metabolic alkalosis.

Question 2 Is it a mixed acid–base disorder?

Answer Yes. On the basis of the respiratory response for metabolic alkalosis, the expected pCO_2 should be ($\Delta HCO_3^- = 13$ (37 − 24) × 0.7 = 13) 53 (40 + 13) mmHg. However, the reported pCO_2 is 59 mmHg. Therefore, the acid–base is metabolic alkalosis superimposed on chronic respiratory acidosis. The coexistence of metabolic alkalosis is due to HCTZ.

Suggesting Reading

Adrogué HJ. Diagnosis and management of severe respiratory acidosis: a 65-year-old man with a double lung transplant and shortness of breath. Am J Kidney Dis. 2010;56:994–1000.

Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders [1 of 2 parts]. N Engl J Med. 1998;338:26–34.

Adrogué HJ, Madias NE. Respiratory acidosis. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 597–639.

Brown LK. Hypoventilation syndromes. Clin Chest Med. 2010;31:249–70.

Bruno CM, Valenti M. Acid-base disorders in patients with chronic obstructive pulmonary disease: a pathophysiological review. J Biomed Biotechnol. 2012;915150 (Article ID 915150, 2012).

Calverley PMA. Respiratory failure in chronic obstructive pulmonary disease. Eur Respir J. 2003;22(Suppl 47):26s–30s.

Davidson AC. Managing acute hypercapnic respiratory failure in adults: where do we need to get to? On behalf of the British Thoracic Society Guideline Group for The ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71:297–8.

Elliott CG, Morris AH. Clinical syndromes of respiratory acidosis and alkalosis. In: Seldin DW, Giebisch G, editors. The regulation of acid-base balance. New York: Raven Press; 1989. p. 483–521.

McFadden ER Jr. Acute severe asthma. Am J Respir Crit Care Med. 2003;68:740–59.

Weinberger SE, Schwartzstein RM, Weiss JW. Hypercapnia. N Engl J Med. 1989;321:1223–31.

Wilson KC, Saukkonen JJ. Acute respiratory failure from abused substances. J Intensive Care Med. 2004;19:183–93.

Chapter 13
Respiratory Alkalosis

The physiology section of Chap. 12 applies to this chapter as well. Respiratory alkalosis, also called primary hypocapnia, is characterized by low pCO_2 (<35 mmHg) and elevated pH (>7.40). Primary hypocapnia reflects alveolar hyperventilation. The resultant alkalinization of body fluids is ameliorated by a decrease in serum [HCO_3^-]. Secondary hypocapnia should be distinguished from primary hypocapnia, as the former occurs in response to metabolic acidosis. As soon as respiratory alkalosis develops, a decrease in serum [HCO_3^-] occurs within minutes. This is due to nonbicarbonate buffering as well as H^+ release from tissues. Lactate is also produced by alkalemia. This buffering from various sources persists for several hours, and the resultant acid–base disturbance is called acute respiratory alkalosis. During acute hypocapnia, the H^+ secretion in both proximal tubule and cortical collecting duct is suppressed. When alkalemia persists, renal compensation starts with a decrease in both H^+ secretion and basolateral exit of HCO_3^- in the proximal tubule. This lowers serum [HCO_3^-] even further, due to which, the pH is maintained close to normal. The full renal compensation takes 2–3 days for completion, and a new steady state is established, which is called chronic respiratory alkalosis.

Pathophysiology

Arterial CO_2 tension represents the balance between its production, elimination, and the inspired CO_2. The inspired CO_2 is negligible. Reduced production of CO_2 can occur in hypothyroidism and hypothermia; however, parallel reduction in alveolar ventilation also occurs. Therefore, respiratory alkalosis is usually not seen in these conditions. For all practical purposes, primary hypocapnia and alkalemia develop due to elimination rather than reduced production of CO_2.

Primary hypocapnia results from alveolar hyperventilation due to increased ventilatory drive. Increased ventilatory drive arises from signals originating from lungs, the peripheral chemoreceptors (carotid and aortic), and the central chemoreceptors

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_13

located in the medullary respiratory center. The response of central chemoreceptors to CO_2 is augmented by pain, anxiety, certain medications (progesterone, salicylates, etc.), and systemic diseases such as sepsis and liver failure. Although hypoxemia is a major stimulus for alveolar hyperventilation, pO_2 values <60 mmHg are required to cause this effect.

Patients on mechanical ventilation may develop respiratory alkalosis due to increased tidal volume and/or respiratory rate. Reduction in either or both may improve hypocapnia and respiratory alkalosis.

Thus, as stated in Chap. 12, both central and peripheral receptors, medullary respiratory center, and respiratory muscles sense change in pCO_2, O_2, and pH and respond appropriately to improve hypocapnia.

Secondary Physiologic Response to Respiratory Alkalosis (Hypocapnia)

As stated earlier, the renal and nonrenal mechanisms respond to a decrease in pCO_2 by lowering HCO_3^-, so that dangerous increases in pH are avoided. Although acute respiratory alkalosis causes high pH, chronic respiratory alkalosis maintains pH at slightly high but near normal levels by further lowering serum [HCO_3^-]. The secondary responses to both acute and chronic respiratory alkalosis are shown below:

Acute respiratory alkalosis For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.2 mEq/L.

Chronic respiratory alkalosis For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.4 mEq/L.

Table 13.1 shows the relationship between pCO_2, expected secondary response (compensation) and arterial pH in acute and chronic respiratory alkalosis.

Table 13.1 Relationship between hypocapnia, renal response, and pH

Type	pCO_2 (mmHg)	Expected renal response (compensation)	Expected serum [HCO_3^-]	pH (calculated from Henderson equation) after compensation
Normal	40	–	24	7.40
Acute	20[a]	For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.2 mEq/L, $\Delta pCO_2 = 20$ $(40 - 20 = 20 \times 0.2 = 4)$	20 $(24 - 4 = 20)$	7.56
Chronic	20[a]	For each mmHg decrease in pCO_2, HCO_3^- decreases by 0.4 mEq/L, $\Delta pCO_2 = 20 (40 - 20 = 20 \times 0.4 = 8)$	16 $(24 - 8 = 16)$	7.50

[a]Arbitrary value

Mechanisms of Secondary Physiologic Response

Acute respiratory alkalosis Hypocapnia decreases H^+ concentration due to low H_2CO_3 concentration. As a result, the pH becomes dangerously high. Immediately the pH is reduced by a decrease in HCO_3^- concentration, which is accomplished by H^+ release from hemoglobin and tissue buffers. Release of H^+ from cells and production of organic acids such as lactic acid largely account for reduction in HCO_3^- concentration. These adaptive changes are complete within 15 min. As shown in Table 13.1, for each mmHg decrease in pCO_2, HCO_3^- decreases by 0.2 mEq/L.

Chronic respiratory alkalosis If hypocapnia persists for few hours, adaptation occurs with further decrease in HCO_3^- concentration. As a result, the pH returns to near normal or slightly above normal. The mechanisms for this change in pH are twofold: (1) net acid excretion, particularly titratable acidity, decreases with no change in NH_4^+ excretion; and (2) HCO_3^- excretion increases. These two mechanisms increase urine pH (alkaline pH). After several days, net acid excretion increases, and HCO_3^- excretion decreases with return of urine pH to control level. As shown in Table 13.1, for each mmHg decrease in pCO_2, HCO_3^- decreases by 0.4 mEq/L in chronic respiratory alkalosis.

Both the decrease and stabilization of HCO_3^- in chronic hypocapnia are related to inhibition of luminal Na/H exchanger and basolateral Na/HCO_3 cotransporter in the proximal tubule. Also, it has been shown that H-ATPase activity throughout the nephron segments is decreased in chronic hypocapnia.

Usually serum Cl^- concentration is increased in chronic respiratory alkalosis. This increase is not due to a decrease in serum HCO_3^- concentration. Studies have attributed the increase in Cl^- to Na^+ excretion without accompanying Cl^- excretion. Also, ECF volume decreases due to Na^+ excretion, which raises Cl^- concentration.

Causes of Acute and Chronic Respiratory Alkalosis

With few exceptions, all causes are associated with both acute and chronic respiratory alkalosis. Acute respiratory alkalosis is generally caused by anxiety–hyperventilation syndrome, pain, pneumonia, acute asthmatic attack, septicemia, pulmonary embolism, pulmonary edema, salicylate ingestion, or increased minute ventilation in mechanically ventilated patients. Therefore, acute respiratory alkalosis is rather common in general wards and intensive care units. Chronic respiratory alkalosis is rather common in patients with central nervous system disorders, interstitial lung diseases, and chronic liver failure. Pregnancy is a condition of chronic respiratory alkalosis. Table 13.2 shows the most important causes of respiratory alkalosis.

Table 13.2 Causes of respiratory alkalosis

Direct stimulation of medullary respiratory center
Anxiety–hyperventilation syndrome
Stroke
CNS infection, tumor, or trauma
Gram-negative sepsis
Liver failure
Pregnancy
Hypermetabolic state (fever, thyrotoxicosis)
Drugs (salicylates, progesterone, nicotine, xanthine derivatives, catecholamines, antipsychotic drug quetiapine)
Pain
Hypoxemic stimulation of medullary respiratory center
Pulmonary diseases (pneumonia, asthma, pulmonary edema, pulmonary embolus, interstitial lung disease, high altitude, hypotension, severe anemia)
Mechanical ventilation
High minute ventilation

Selected Conditions of Respiratory Alkalosis

Anxiety–Hyperventilation Syndrome Some individuals overbreathe in response to stressful situations and develop hypocapnia and respiratory alkalosis. Anxiety and or panic disorders (symptoms may overlap between the two conditions) may provoke hyperventilation. Patients present with symptoms such as dyspnea, circumoral numbness, paresthesias of lower extremities, and chest tightness or pain. Interestingly, these anxious individuals with dyspnea are not hypoxemic, and they have adequate oxygenation. Hyperventilation syndrome can be either acute or chronic. Arterial blood gasses are extremely important to exclude other causes of hyperventilation and hypoxia. In particular, subclinical asthma should be ruled out based on blood gas measurements.

The pathogenesis of hyperventilation syndrome is not completely understood. However, certain factors such as sodium lactate, CO_2, caffeine, isoproterenol, and emotional stress have been implicated in provoking hyperventilation.

Treatment for acute episodes includes anxiolytic drugs, psychiatric counseling, and reassurance. Serotonin reuptake inhibitors are frequently used for chronic patients.

High Altitude As the person climbs from sea level to high altitude, both alveolar and arterial O_2 pressure fall, and hypoxemia develops. Within few minutes, alveolar ventilation increases with a slight reduction in pCO_2. In hours to 2–3 days, adaptation to high altitude occurs by progressive increase in ventilation. This increase in ventilation is related to stimulation of peripheral chemoreceptors located in the carotid and aortic arch bodies (carotid body receptors are more sensitive than aortic arch body receptors to hypoxemia), which send signals to the medullary respiratory

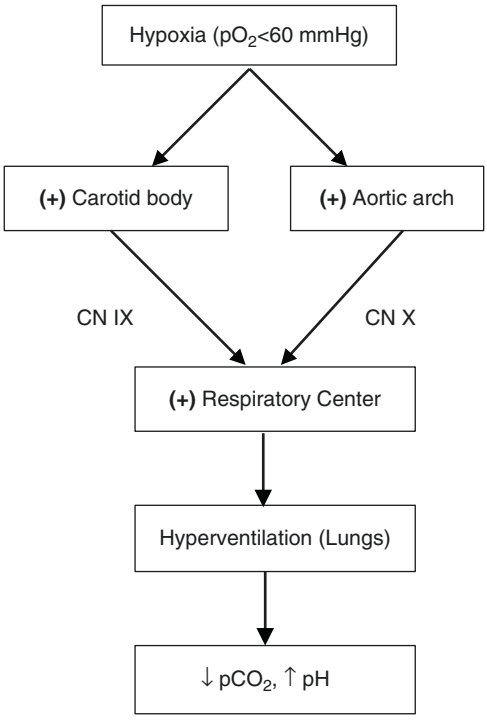

Fig. 13.1 Hypoxic stimulation of medullary respiratory center causing hyperventilation. CN IX 9th cranial nerve (glossopharyngeal nerve), CN X 10th cranial nerve (vagus nerve); + indicates stimulation

centers. Hyperventilation does not continue forever because the stimulatory effect of peripheral chemoreceptors to hypoxemia is slowly reduced. Either low pCO_2 or low concentration of bicarbonate in cerebrospinal fluid seems to desensitize the peripheral chemoreceptors. As a result, long-term residents living in high altitude areas maintain low alveolar ventilation and high pCO_2 for any given pO_2 level compared to short-term dwellers. Figure 13.1 shows the mechanism of hypoxia-induced alveolar hyperventilation.

Drugs Salicylates, theophylline, nicotine, progesterone, medroxyprogesterone, nikethamide, and other drugs (Table 13.2) stimulate respiratory center and increase alveolar ventilation. Salicylates cause mixed respiratory alkalosis and metabolic acidosis (Chap. 7). Progesterone is an important hormone in normal and pregnant women. Respiratory alkalosis is a consistent acid–base disorder in pregnant women because of high circulating levels of progesterone. Progesterone levels are also high in nonpregnant women, which account for slightly lower serum HCO_3 concentration in women than men. Modest beneficial effects of progesterone and medroxyprogesterone have been observed in the management of hypercapnia.

Central Nervous System (CNS) Diseases Hypocapnia due to hyperventilation is quite common in CNS disorders. Three patterns of hyperventilation are observed: (1) central hyperventilation is seen, for example, in patients with increased

intracranial pressure. It is characterized by a regular rhythm and increased rate and depth of breathing; (2) Cheyne-Stokes respiration, seen in patients with bilateral cerebral hemispheric lesions, is characterized by alternating hyperventilation and apnea; and (3) Biot or cluster breathing is characterized by groups of quick, shallow inspirations followed by regular or irregular periods of apnea. This type of breathing is seen in diseases of pons due to trauma or stroke.

Pulmonary Diseases Hypocapnia and respiratory alkalosis are frequent manifestations of various pulmonary diseases. In many of these diseases, hypocapnia is independent of hypoxemia. Afferent signals arising from the lung are sent via the vagus and glossopharyngeal nerves to the respiratory center. Three types of receptors are responsible for the afferent signals. These are (1) irritant (nociceptive) receptors, (2) stretch receptors, and (3) J (juxtacapillary) receptors. All these receptors respond appropriately and send signals to the medullary respiratory center with resultant hyperventilation.

Sepsis Hyperventilation and respiratory alkalosis are rather common in sepsis because of such stimuli as fever, hypotension, or hypoxemia. However, hyperventilation in gram-negative septicemia seems to be independent of these stimuli. It was suggested that bacterial toxins (lipopolysaccharides) stimulate central chemoreceptors, causing hyperventilation.

Liver Disease Respiratory alkalosis is the most common acid–base disorder in patients with liver failure and hepatic encephalopathy. Hyperventilation seems to be related to increased levels of progesterone, NH_3, and brain hypoxia. Interestingly, increased NH_3 levels correlate best with the degree of hypocapnia in patients with liver disease.

Pregnancy Progesterone levels increase during pregnancy, which stimulate the central chemoreceptors and cause hyperventilation and respiratory alkalosis. During the third trimester, arterial pCO_2 levels may decrease to 28–30 mmHg because of very high circulating progesterone levels.

Clinical Manifestations

Acute Respiratory Alkalosis

When pCO_2 is lowered acutely, paresthesias of lower extremities, circumoral numbness, tingling of hands, mouth, and a feeling of chest tightness occur. Headache, light headedness, confusion, and disorientation are also common. Severe alkalosis may precipitate seizures and cardiac arrhythmias. These manifestations are related to central nervous system (CNS), cardiovascular, and metabolic effects.

CNS Effects Acute hypocapnia causes sudden decrease in brain blood flow due to cerebral vasoconstriction. This results in a decrease in intracranial and intraocular pressures.

- Light headedness, confusion, and other manifestations are related to decreased cerebral perfusion.
- Electroencephalogram (EEG) changes such as slowing and high-voltage wave forms also occur.
- Acid–base changes are similar in both cerebrospinal fluid (CSF) and systemic blood during acute hypocapnia.
- Acral paresthesias are due to decreased blood flow to the skin.

Cardiovascular Effects Acute hypocapnia decreases myocardial blood flow and O_2 supply.

- Cardiac output is decreased.
- Coronary vasoconstriction and chest pain occur.
- Cardiac arrhythmias are common with severe hypocapnia.

Metabolic Effects Both lactate and ketoacid production are increased.

- A decrease in plasma volume is observed.
- Acute hypocalcemia due to increased binding of Ca^{2+} to albumin can occur with precipitation of tetany and perioral tingling.
- Mild hyponatremia, hypokalemia, and hypophosphatemia may be present due to cellular shift.

Chronic Respiratory Alkalosis

Individuals with chronic respiratory alkalosis are generally less symptomatic than subjects with acute respiratory alkalosis. Hyperventilation is subtle in many patients, and it is not even recognized by patients and clinicians. However, certain CNS, cardiovascular, and metabolic effects do occur in patients with chronic respiratory alkalosis.

CNS Effects CSF pH rises when pCO_2 is sufficiently low.

- CSF lactate levels may be high (alkalosis-induced).
- Light headedness may be common.

Cardiovascular Effects Common in individuals who climb mountains and live at high altitudes. These effects are:

- Initially, cardiac output increases due to a decrease in peripheral vascular resistance.
- Heart rate goes up.
- Blood pressure remains normal secondary to decreased peripheral vascular resistance.

- Cardiac output returns to baseline 1–6 weeks after exposure to high altitude, but heart rate remains elevated.
- Blood flow to the kidneys and skin is reduced.
- Both blood and plasma volumes are reduced due to renal Na^+ loss; however, after several days of high altitude exposure, only blood volume returns to normal due to an increase in hemoglobin and hematocrit increase.
- All of the above, manifestations are related to hypoxemia.

Metabolic Effects In addition to low plasma volume, hyponatremia, hypokalemia, and hypophosphatemia due to cellular shifts are common. Decreased ionized Ca^{2+} is also common, causing tetany, Chvostek's and Trousseau's signs.

Diagnosis

History and physical examination can provide useful information about the causes of both acute and chronic respiratory alkalosis.

History of pain, anxiety, drug use, or pregnancy can easily be obtained. Pulmonary causes of respiratory alkalosis should be addressed. Hyperventilation in patients on ventilators can be recognized from settings of the ventilators.

Pertinent physical examination findings are summarized in Table 13.3.

Laboratory results:

Table 13.3 Physical examination and possible cause of respiratory alkalosis

Examination	Clinical cause (clue)
Vital signs	
Hypotension	Hypoxemia
↑ Heart rate	Fever, anxiety
Orthostatic changes	↓ Plasma volume
↑ Temperature	Infection or sepsis
Tachypnea	Arrhythmias, hypoxemia, pulmonary disease
Lungs	
Inspiratory crackles	Pulmonary edema
Inspiratory rhonchi and crackles	Pulmonary fibrosis
Tachypnea, pulmonary rub	Pulmonary embolism
Prolonged expiratory wheezing	Asthma
Heart	
Irregular rhythm	Arrhythmias
↑ P_2, palpable P_2, right ventricular heave	Pulmonary hypertension
Abdomen	
Ascites, asterixis	Liver disease
Gravid uterus	Pregnancy
Extremities	
Cyanosis	Hypoxemia
Neurologic	
Tremor, paresthesias	Anxiety, low blood flow to skin
Muscle weakness	Hypokalemia, hypophosphatemia
Chvostek's and Trousseau's signs	Low ionized Ca^{2+}

Arterial Blood Gas (ABG)

- Respiratory alkalosis is characterized by low pCO_2, low serum [HCO_3^-], and high pH. In acute respiratory alkalosis, serum [HCO_3^-] is around 20 mEq/L, because the secondary response to hypocapnia of 20 mmHg is a decrease of 4 mEq/L from normal [HCO_3^-] of 24 mEq/L.
- On the other hand, the serum [HCO_3^-] from normal level of 24 mEq/L drops to 16 mEq/L in chronic respiratory alkalosis for the same hypocapnia of 20 mmHg.
- Note that without pH, it is sometimes difficult to differentiate between hyperchloremic metabolic acidosis from chronic respiratory alkalosis, because both of them have hyperchloremia.

Lab Tests

- Persistent hyponatremia, hypokalemia, hypophosphatemia, and low ionized Ca^{2+}—suggestive of chronic respiratory alkalosis
- ↑ WBC—suggestive of infectious process
- ↓ Hemoglobin—suggestive of anemia
- ↑ Hematocrit—suggestive of exposure to high altitude
- Abnormal liver function tests—liver disease
- ↑ T_3 and T_4 and low TSH—suggestive of hyperthyroidism
- When both respiratory alkalosis and high AG metabolic acidosis are present—suspect salicylate intake
- Positive urine β-human chorionic hormone—pregnancy

Other Tests

- Chest x-ray
- Blood cultures

Treatment

- Respiratory alkalosis is not benign and no longer self-limited. Treatment is, therefore, warranted.
- Correction of the primary disorder of the respiratory alkalosis is extremely important.
- Table 13.4 shows the cause-specific treatment of respiratory alkalosis.

Table 13.4 Treatment of respiratory alkalosis

Cause	Treatment options
Anxiety–hyperventilation syndromes	Rebreathing into a paper or plastic bag, mild sedation, and reassurance
Hypoxia	O_2
Salicylates	Urinary alkalinization, forced diuresis, dialysis
Sepsis	Antibiotics
Hyperthyroidism	β-blockers, antithyroid medications
Asthma	Bronchodilators, corticosteroids
Pneumonia	Antibiotics
Pulmonary edema	Diuretics, improvement in CHF
Pulmonary embolism	O_2, anticoagulation
Cardiac arrhythmias	Lower pH <7.50, acetazolamide, rebreather
High altitude, climbing	O_2, acetazolamide
Mechanical ventilation	↓ Ventilatory rate and tidal volume, ↑ dead space, mild sedation without skeletal muscle paralysis

Study Questions

Case 1 A 24-year-old woman with asthma is seen in the Emergency Department (ED) for acute exacerbation due to upper respiratory tract infection. Prior to bronchodilator and corticosteroid therapy, laboratory results were drawn, which show:

Serum	ABG
Na^+ = 139 mEq/L	pH = 7.55
K^+ = 3.4 mEq/L	pCO_2 = 22 mmHg
Cl^- = 96 mEq/L	pO_2 = 88 mmHg
HCO_3^- = 21 mEq/L	HCO_3^- = 20 mEq/L
Creatinine = 0.6 mg/dL	
BUN = 18 mg/dL	
Glucose = 92 mg/dL	

Question 1 What is the acid–base disturbance?

Answer Based on alkaline pH, low HCO_3^-, and low pCO_2, the acid–base disturbance is respiratory alkalosis.

Question 2 Is it acute or chronic respiratory alkalosis?

Answer It is acute respiratory alkalosis, as the decrease in serum [HCO_3^-] from 24 to 21 mEq/L (for each mmHg decrease in pCO_2, HCO_3^- decreases by 0.2 mEq/L) is consistent with uncomplicated acute respiratory alkalosis. Hypocapnia due to hyperventilation is common during exacerbation of asthma.

Case 2 A 66-year-old man with chronic obstructive pulmonary disease is admitted for increasing shortness of breath and swollen legs for 10 days. He is on bronchodilators and furosemide. Physical examination reveals crackles and an S_3 and 2+ pitting edema in lower extremities. The patient receives i.v. furosemide 60 mg Q12H for 3 days, and his shortness of breath and edema improved. Electrocardiography is normal. Laboratory results:

Serum electrolytes and ABG—on admission	Serum electrolytes and ABG—on the 4th day
Na^+ = 136 mEq/L	Na^+ = 134 mEq/L
K^+ = 3.3 mEq/L	K^+ = 3.2 mEq/L
Cl^- = 104 mEq/L	Cl^- = 96 mEq/L
HCO_3^- = 18 mEq/L	HCO_3^- = 21 mEq/L
Creatinine = 1.1 mg/dL	Creatinine = 1.2 mg/dL
BUN = 28 mg/dL	BUN = 38 mg/dL
Glucose = 102 mg/dL	Glucose = 112 mg/dL
ABG	
pH = 7.45	pH = 7.48
pCO_2 = 26 mmHg	pCO_2 = 28 mmHg
pO_2 = 90 mmHg	pO_2 = 92 mmHg
HCO_3^- = 17 mEq/L	HCO_3^- = 20 mEq/L

Question 1 What is the acid–base disturbance on admission?

Answer Based on alkaline pH, low serum [HCO_3^-], and pCO_2, the acid–base disturbance is respiratory alkalosis. The expected serum [HCO_3^-] from secondary response for acute respiratory alkalosis is 21 mEq/L (24 − 3 = 21 mEq/L). For chronic respiratory alkalosis, the expected serum [HCO_3^-] from secondary response is 18 (24 − 6 = 18 mEq/L). Therefore, the patient has uncomplicated chronic respiratory alkalosis.

Question 2 What is the acid–base disorder on the 4th day?

Answer Although the patient had chronic respiratory alkalosis on admission, the pH, serum [HCO_3^-], and pCO_2 are elevated following treatment, suggesting superimposed metabolic alkalosis caused by administration of furosemide. The induction of metabolic alkalosis due to loop diuretics is not uncommon in patients with congestive heart failure and edema.

Suggested Reading

Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders [1 of 2 parts]. N Engl J Med. 1998;338:26–34.

Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care. 2010;14:220.

Elliott CG, Morris AH. Clinical syndromes of respiratory acidosis and alkalosis. In: Seldin DW, Giebisch G, editors. The regulation of acid-base balance. New York: Raven Press; 1989. p. 483–521.
Krapf R, Hulter HN. Respiratory alkalosis. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid-base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 641–79.
Laffey JG, Kavanagh BP. Hypocapnia. N Engl J Med. 2002;347:43–53.
Palmer BF. Evaluation and treatment of respiratory alkalosis. Am J Kidney Dis. 2012;60:834–8.
Vassilakopoulos T. Control of ventilation and respiratory muscle. In: Spiro SG, Silvestri GA, Agusti A, editors. Clinical respiratory medicine. 4th ed. Philadelphia: Elsevier, Inc; 2012. p. 50–62.
Vollmer LL, Strawn JR, Sah R. Acid-base dysregulation and chemosensory mechanisms in panic disorder: a translational update. Transl Psychiatry. 2015;5:e572.

Chapter 14
Mixed Acid–Base Disorders

A mixed acid–base disorder is defined as the coexistence of two or three primary disorders in the same patient. These disorders can occur simultaneously or at different times. Two groups of patients are at risk for mixed acid–base disturbances: the critically ill patients in the intensive care units and the elderly. Also, diabetic or alcoholic subjects may present to the Emergency Department with a double or triple acid–base disturbance.

In general, the critically ill patients have multiple medical conditions that can elicit a mixed acid–base disturbance. For example, a septic or liver failure patient can present initially with a respiratory alkalosis and subsequently develops a high anion gap (AG) metabolic acidosis due to hypotension. The other group of patients, the elderly, may have a chronic disease such as chronic obstructive pulmonary disease (COPD) with respiratory acidosis and subsequent development of metabolic alkalosis due to a thiazide or loop diuretic for treatment of cor pulmonale.

Recognition of a mixed acid–base disorder by the clinician is extremely important for appropriate care of the patient. For example, failure to recognize the metabolic alkalosis superimposed on chronic respiratory acidosis may aggravate hypoxemia because both disorders are associated with an increase in pCO_2. Also, vigorous saline administration may improve the underlying metabolic alkalosis while lowering the pH to a dangerous level. To avoid these changes, it is extremely important to recognize both disorders and treat them simultaneously so that the patient's condition would ultimately improve.

Furthermore, identification of a mixed acid–base disorder may provide a clue to the onset of a new condition, particularly in a critically ill patient. For example, a patient with severe pneumonia and respiratory alkalosis may start developing an increase in AG within a few hours of admission. This suggests that the patient may be generating lactic acid due to septic shock.

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_14

Analysis of Mixed Acid–Base Disorders

Mixed acid–base disorders should be suspected whenever (see also Chap. 4):

1. There is no compensatory response or overcompensation for a primary simple acid–base disorder
2. The pH and [HCO_3^-] are normal, but the AG is high (mixed metabolic acidosis and metabolic alkalosis)
3. The pH is near normal, but [HCO_3^-] is low (mixed metabolic acidosis and respiratory alkalosis)
4. The pH is low (<7.4), but [HCO_3^-] is normal or slightly low (mixed metabolic acidosis and respiratory acidosis)
5. The pH is near normal, but [HCO_3^-] is high (mixed metabolic alkalosis and respiratory acidosis)
6. The pH is high (>7.4), but [HCO_3^-] is normal (mixed metabolic alkalosis and respiratory alkalosis)

Several factors should be taken into consideration in analyzing a mixed acid–base disorder. Such factors include:

1. Medical and clinical settings: stable or unstable, intubation, sepsis, hypotension, nasogastric suction, or ketoacidosis, etc
2. Drug administration: sedation
3. Evaluation of pH: lower than before (additive), or normal (counterbalancing), or high (additive)
4. AG: normal or high
5. Time course of pH changes: acute or chronic disturbance

The following discussion will focus on the clinical settings in which a common mixed acid–base disorder occurs with characteristic electrolyte and arterial blood gas (ABG) values. Note that these laboratory values vary depending on the presence of dominant disturbance and the duration of the coexisting disorder. Table 14.1 summarizes the most frequently observed mixed acid–base disorders in hospitalized patients.

Metabolic Acidosis and Metabolic Alkalosis

This disorder can be seen in two clinical settings:

1. Metabolic acidosis due to chronic kidney disease (CKD) stages 4 and 5 (renal failure), or ketoacidosis, or lactic acidosis with a superimposed metabolic alkalosis due to vomiting, or nasogastric suction. The most compatible electrolyte and ABG values are as follows:

Table 14.1 Common mixed acid–base disorders, pH and electrolyte profiles

Acid–base disorder	Clinical setting	pH	pCO_2[a]	Na^+	K^+	Cl^-	HCO_3^-[a]	AG
Double acid–base disorders								
Metabolic acidosis and metabolic alkalosis	Renal failure (CKD 4 and 5), diabetic ketoacidosis, lactic acidosis with vomiting, or diuretics	N	N	N/↓	N↓	N↓	~N	↑
Metabolic acidosis and respiratory alkalosis	Renal failure (CKD 4 and 5) with sepsis, or salicylate intoxication, or pulmonary embolus	~N	↓↓	N	N	N/↑	↓↓	↑ or N[b]
Metabolic acidosis and respiratory acidosis	Cardiac arrest or renal failure with emphysema, or sedatives, or narcotics	↓↓	N/↑	N	N	N	N/↓	↑ or N[b]
Metabolic alkalosis and respiratory alkalosis	Vomiting, diuretics with pneumonia, or hepatic failure, or pregnancy	↑↑	N/↓	~ N	↓	N	N/↑	Slight↑
Metabolic alkalosis and respiratory acidosis	Vomiting or diuretics with emphysema, or sedatives	N/↑	↑↑	N/↓	N/↓	N	↑↑	N
Triple acid–base disorders								
Metabolic acidosis, metabolic alkalosis, and respiratory alkalosis	Ketoacidosis with vomiting and abdominal pain, or pneumonia	↑	↓	N	N/↓	N/↓	Slight↓	↑
Metabolic acidosis, metabolic alkalosis and respiratory acidosis	Ketoacidosis with vomiting, or sedative, or COPD	↓↓	↓	N	N	N	↓↓	↑

AG anion gap, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease
[a]Concentrations of these vary depending on the severity of the dominant acid–base disorder
[b]AG depends on the etiology of metabolic acidosis

Serum	ABG
Na^+ = 138 mEq/L	pH = 7.39
K^+ = 3.6 mEq/L	pCO_2 = 39 mmHg
Cl^- = 96 mEq/L	pO_2 = 92 mmHg
HCO_3^- = 23 mEq/L	HCO_3^- = 22 mEq/L
Creatinine = 4.6 mg/dL	
BUN = 48 mg/dL	
AG = 19	

ABG arterial blood gas, *AG* anion gap, *BUN* blood urea nitrogen

2. Metabolic alkalosis due to loop or thiazide diuretic use with a superimposed metabolic acidosis due to ketoacidosis or renal failure. Compatible laboratory results are:

Serum	ABG
Na^+ = 130 mEq/L	pH = 7.41
K^+ = 3.2 mEq/L	pCO_2 = 41 mmHg
Cl^- = 86 mEq/L	pO_2 = 92 mmHg
HCO_3^- = 25 mEq/L	HCO_3^- = 24 mEq/L
Creatinine = 1.4 mg/dL	
BUN = 28 mg/dL	
AG = 19	

ABG arterial blood gas, *AG* anion gap, *BUN* blood urea nitrogen

Note that electrolyte and ABG values vary depending on the dominant acid–base disorder. The effect on pH by these acid–base disorders is to bring it to near normal (counterbalancing). One consistent abnormality is serum AG, which is elevated. If diarrhea is the cause for metabolic acidosis, the AG may not be that high.

Metabolic Acidosis and Respiratory Alkalosis

The clinical setting is usually renal failure, ketoacidosis, or lactic acidosis with sepsis. Salicylate overdose or pulmonary embolism can produce both metabolic acidosis and respiratory alkalosis. The representative electrolyte and ABG are shown in the following table. The AG is elevated. The effect on pH is counterbalancing, so that the pH is brought to near normal, but the fall in pCO_2 is greater with both disorders. In salicylate overdose, the initial acid–base disorder is respiratory alkalosis due to direct central nervous system (CNS) stimulation followed by the development of metabolic acidosis. The presence of dominant disorder can be identified by calculation of appropriate secondary response. For example, if metabolic acidosis is the dominant acid–base disorder, the superimposed respiratory alkalosis can be diagnosed by a greater fall in pCO_2 than expected for a simple metabolic acidosis. If respiratory alkalosis is the dominant disturbance, a coexisting metabolic acidosis can be identified by a greater fall in serum [HCO_3^-] than expected for a simple respiratory alkalosis.

The laboratory values shown in the following table indicate that metabolic acidosis is the dominant acid–base disturbance. The expected pCO_2 should be 26 ± 2 mmHg (1.5 × serum HCO_3^- + 8 ± 2 = 18 + 8 = 26 ± 2). Instead, the reported pCO_2 is 22 mmHg, indicating that the patient is more hypocapnic than expected. Thus, respiratory alkalosis is superimposed on metabolic acidosis.

Serum	ABG
Na^+ = 129 mEq/L	pH = 7.36
K^+ = 3.4 mEq/L	pCO_2 = 22 mmHg
Cl^- = 92 mEq/L	pO_2 = 90 mmHg
HCO_3^- = 12 mEq/L	HCO_3^- = 11 mEq/L
Creatinine = 8.6 mg/dL	
BUN = 68 mg/dL	
AG = 25	

ABG arterial blood gas, *AG* anion gap, *BUN* blood urea nitrogen

Metabolic Acidosis and Respiratory Acidosis

This acid–base disorder occurs in the clinical setting of cardiac arrest, renal failure, or lactic acidosis with sedatives or narcotics, or COPD. The effect on pH is additive, as both acid–base disorders lower pH. The electrolyte pattern and ABG (see table below) suggest that the primary acid–base disorder is chronic respiratory acidosis and the coexisting disturbance is metabolic acidosis due to lactic acidosis. The AG is high. The AG may be normal, if the cause of metabolic acidosis is diarrhea or renal tubular defect.

Serum	ABG
Na^+ = 136 mEq/L	pH = 7.27
K^+ = 3.9 mEq/L	pCO_2 = 44 mmHg
Cl^- = 100 mEq/L	pO_2 = 88 mmHg
HCO_3^- = 20 mEq/L	HCO_3^- = 19 mEq/L
Creatinine = 1.0 mg/dL	
BUN = 24 mg/dL	
AG = 16	

ABG arterial blood gas, *AG* anion gap, *BUN* blood urea nitrogen

Metabolic Alkalosis and Respiratory Alkalosis

The conditions that predispose to this mixed acid–base disorder are vomiting or diuretic therapy with metabolic alkalosis complicated by respiratory alkalosis due to pneumonia or hepatic failure. Pregnant individuals usually have respiratory alkalosis because of progesterone and elevated diaphragm; however, when they develop profuse vomiting, a superimposed metabolic alkalosis develops.

When patients on mechanical ventilator develop respiratory alkalosis because of increased respiratory rate, they are predisposed to metabolic alkalosis, if nasogastric suction is applied. The effect on pH is additive. The following electrolyte and ABG pattern was observed in a patient with alkali ingestion and pneumonia:

Serum	ABG
Na^+ = 146 mEq/L	pH = 7.60
K^+ = 2.8 mEq/L	pCO_2 = 45 mmHg
Cl^- = 80 mEq/L	pO_2 = 68 mmHg
HCO_3^- = 52 mEq/L	HCO_3^- = 51 mEq/L
Creatinine = 1.6 mg/dL	
BUN = 24 mg/dL	
AG = 14	

ABG arterial blood gas, *AG* anion gap, *BUN* blood urea nitrogen

The AG is elevated because of alkalosis-induced lactate production.

Metabolic Alkalosis and Respiratory Acidosis

The clinical setting in patients with mixed metabolic alkalosis and respiratory acidosis is vomiting or diuretic use with COPD, or sedatives, or narcotics that inhibit the medullary respiratory center. This disorder is commonly seen in patients with COPD, hypertension, and congestive heart failure (CHF), who are treated with either loop or thiazide diuretics. The effect on pH is counterbalancing. The following electrolytes and ABG are consistent in a patient with chronic respiratory acidosis and diuretic therapy for hypertension.

Serum	ABG
Na^+ = 134 mEq/L	pH = 7.42
K^+ = 3.6 mEq/L	pCO_2 = 59 mmHg
Cl^- = 91 mEq/L	pO_2 = 62 mmHg
HCO_3^- = 37 mEq/L	HCO_3^- = 36 mEq/L
Creatinine = 1.3 mg/dL	
BUN = 18 mg/dL	

ABG arterial blood gas, *AG* anion gap, *BUN* blood urea nitrogen

Two other mixed acid–base disorders are seen clinically, but infrequently. They are:

1. *Hyperchloremic (non-AG) metabolic acidosis and high AG metabolic acidosis*
   The clinical setting is a patient with profuse diarrhea who subsequently develops hypotension and lactic acidosis. The effect on pH is additive. Typical laboratory results are as follows:

$$\text{pH} = 7.10$$
$$pCO_2 = 18 \text{ mmHg}$$
$$pO_2 = 86 \text{ mmHg}$$
$$\text{Serum } \left[HCO_3^-\right] = 6 \text{ mEq/L}$$
$$\text{Calculated } \left[HCO_3^-\right] = 5 \text{ mEq/L}$$
$$\text{AG} = \text{elevated}$$

2. *Acute respiratory acidosis and chronic respiratory acidosis*
   The clinical setting is a COPD patient with chronic respiratory acidosis, who develops deterioration in his/her lung disease, or application of a sedative or high inspired O_2. The effect on pH is additive. Typical laboratory results are as follows:

$$\text{pH} = 7.31$$
$$\text{pCO}_2 = 80 \text{ mmHg}$$
$$\text{pO}_2 = 70 \text{ mmHg}$$
$$\text{Serum } \left[\text{HCO}_3^-\right] = 39 \text{ mEq/L}$$
$$\text{Calculated } \left[\text{HCO}_3^-\right] = 38 \text{ mEq/L}$$
$$\text{AG} = \text{normal}$$

The ABG suggests respiratory acidosis. However, the observed HCO_3^- is higher than for both acute (expected HCO_3^- = 28 mEq/L) and chronic (expected HCO_3^- = 36 mEq/L) respiratory acidosis, suggesting acute superimposed on chronic respiratory acidosis. Metabolic alkalosis also increases both pCO_2 and HCO_3^-, but the pH also is elevated. The typical pH in patients with acute respiratory acidosis superimposed on chronic respiratory acidosis is much lower than that of a patient with chronic respiratory acidosis, which is usually >7.34. The pCO_2 of 80 mmHg is not consistent with chronic respiratory acidosis alone.

Triple Acid–Base Disorders

Although less common, triple acid–base disorders can be seen in certain critically ill patients. For example, a patient with ketoacidosis with vomiting and abdominal pain can present with high AG metabolic acidosis, metabolic alkalosis, and respiratory alkalosis (see Case 2).

Similarly, a patient with lactic acidosis, who is on a ventilator with low tidal volume and low respiratory rate and nasogastric suction, typically develops high AG metabolic acidosis, metabolic alkalosis, and respiratory acidosis (see Case 3).

Treatment

Treatment of a mixed acid–base disorder is difficult compared to that of a simple acid–base disorder. Identification of a dominant acid–base disorder and its cause is extremely important. Furthermore, treatment is guided by attention to the blood pH, because therapy of one disturbance of mixed acid–base disorder may not aggravate the other coexisting disturbance. Treatment of common mixed disturbances is outlined in the following sections.

Metabolic Acidosis and Metabolic Alkalosis

- Normal (0.9%) saline improves Cl^- -responsive metabolic alkalosis. If metabolic acidosis is due to diabetic ketoacidosis, insulin and normal (or 0.45% NaCl) will improve ketoacidosis. If ketoacidosis is related to starvation or alcohol, glucose infusion (D5W) is sufficient. For lactic acidosis and metabolic alkalosis, normal saline is effective. In patients with renal failure, metabolic acidosis can be improved by renal replacement therapies.

Metabolic Acidosis and Respiratory Alkalosis

- Correcting the cause of both disorders improves the acid–base disturbance. Administration of $NaHCO_3$ may not be helpful all the time, because it may worsen alkalemia. Rebreather may alleviate respiratory alkalosis.
- Renal replacement therapy improves both acidosis and alkalosis.

Metabolic Acidosis and Respiratory Acidosis

- Both disorders lower pH below 7.1. The cause for respiratory failure should be addressed, and if necessary, intubation should be considered. Hyperventilation and lowering pCO_2 judiciously improve pH. The goal pH is 7.20–7.28.

Metabolic Alkalosis and Respiratory Alkalosis

- Both disorders increase pH above 7.50. If respiratory alkalosis is new, the cause such as sepsis or unrecognized pulmonary embolus should be addressed. A patient on ventilator and nasogastric suction can be managed efficiently to improve both disorders.
- $NaHCO_3$ therapy should be avoided.
- Normal saline, or KCl, or both can improve Cl^- responsive metabolic alkalosis.

Metabolic Alkalosis and Respiratory Acidosis

- Cl^- responsive metabolic alkalosis responds to normal saline and/or KCl. This treatment promotes renal excretion of HCO_3^- and lowers pH.
- Lowering pCO_2 too much worsens alkalemia. Also, vigorous saline administration lowers pH. In order to maintain reasonable pH and pCO_2, it is important to identify the dominant disorder and treat that disorder appropriately. Addressing

the other disorder, if necessary, results in proper management of this mixed acid–base disturbance.
- Patients with chronic respiratory acidosis depend on acidemia for ventilatory drive, rapid increase in their pH should be avoided.

Study Questions

Case 1 For each set of laboratory data, select the appropriate acid–base disturbance:

Option	Na^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	pH	pCO_2 (mmHg)	HCO_3^{-a} (mEq/L)
A	130	95	10	7.34	19	9
B	136	94	24	7.39	39	23
C	130	85	29	7.50	36	28
D	140	100	20	7.27	44	19
E	142	100	32	7.41	52	31

[a]Calculated HCO_3^-

1. Metabolic alkalosis and respiratory acidosis
2. Metabolic acidosis and respiratory alkalosis
3. Metabolic acidosis and respiratory acidosis
4. Metabolic acidosis and metabolic alkalosis
5. Metabolic alkalosis and respiratory alkalosis

Answers A = 2; B = 4; C = 3; D = 5; E = 1 or (1 = E; 2 = A; 3 = D; 4 = B; 5 = C.

To answer these questions, it is important to calculate the AG. The AG and an understanding of the pathogenesis of previously mentioned mixed acid–base disorders provide important clues for their identification. The AG for options A–E is 25, 18, 16, 20, and 10 mEq/L, respectively. Regarding the pathogenesis of the acid–base disorder in Answer 1, either vomiting or diuretic (thiazide or loop diuretic) use generally causes metabolic alkalosis and emphysema or any disorder causing retention of CO_2 results in respiratory acidosis. Laboratory data shown in option E are consistent with metabolic alkalosis and respiratory acidosis. The combination of both disorders have a normal to high pH, elevated HCO_3^-, and pCO_2. The AG is usually normal or slightly elevated, if metabolic alkalosis predominates.

The acid–base disturbance given in Answer 2 may be caused by diseases such as renal failure, lactic acidosis, ketoacidosis, or ingestion of toxins such as methanol or ethylene glycol, which lower serum [HCO_3^-] and elevate AG. The appropriate response for metabolic acidosis is hyperventilation. This results in low pCO_2. Data shown in option A are consistent with metabolic acidosis and respiratory alkalosis. Metabolic acidosis may exist alone (pure) or may exist with another primary disorder (mixed). In order to distinguish between the two disorders, the expected PCO_2 should be calculated, as shown under the discussion of mixed metabolic acidosis and respiratory alkalosis. If the ABG shown in option A were a pure metabolic

acidosis, the pCO_2 would have been between 21 and 25 mmHg. Instead, the pCO_2 is 19 mmHg. Therefore, respiratory alkalosis is superimposed on metabolic acidosis.

The acid–base disturbance given in Answer 3 is generally caused by a condition that generates lactic acid acutely, such as sudden cardiac arrest, seizures, or severe hypotension superimposed on a patient with underlying emphysema with CO_2 retention. The combination of metabolic acidosis and respiratory acidosis lowers pH below 7.40 and [HCO_3^-] below 24 mEq/L with normal to slightly elevated pCO_2. The AG is usually elevated because of accumulation of lactic acid or a similar anion. Laboratory data shown in option D are consistent with both metabolic and respiratory acidosis.

The acid–base disorder given in Answer 4 occurs in a patient with renal failure who develops vomiting, or on a thiazide, or loop diuretic. Renal failure causes high AG metabolic acidosis with low pH, low [HCO_3^-], and low pCO_2. On the other hand, metabolic alkalosis results in a high pH, elevated [HCO_3^-], and a high pCO_2 due to hypoventilation. When both disorders coexist, the pH, [HCO_3^-], and pCO_2 may appear normal. The only clue to this acid–base disorder is elevated AG, because both metabolic acidosis and metabolic alkalosis cause elevated AG. However, metabolic acidosis due to diarrhea or renal tubular acidosis does not elevate AG. The combination of normal AG metabolic acidosis and metabolic alkalosis generally causes slight elevation in AG because of the latter acid–base disorder. Laboratory data shown in option B are consistent with metabolic acidosis and metabolic alkalosis.

The acid–base disturbance given in Answer 5 is seen in a patient who has liver failure with hyperventilation. This causes respiratory alkalosis. If this patient is also being treated with a diuretic, such as furosemide, or has experienced vomiting, the patient develops metabolic alkalosis. In such a patient, the pH is usually >7.40, the [HCO_3^-] is normal to high, and pCO_2 is normal to slightly low. Laboratory data shown in option C are consistent with respiratory and metabolic alkalosis. A similar acid–base disorder can be seen in a normal pregnant woman with severe vomiting.

Case 2 A 38-year-old man with history of type 1 diabetes and pancreatitis is admitted for nausea, vomiting, and severe abdominal pain for the last 4 days. He did not take insulin because of poor oral intake. Laboratory results are as follows:

Serum	ABG
Na^+ = 120 mEq/L	pH = 7.47
K^+ = 3.9 mEq/L	pCO_2 = 23 mmHg
Cl^- = 60 mEq/L	pO_2 = 109 mmHg
HCO_3^- = 17 mEq/L	HCO_3^- = 16 mEq/L
Creatinine = 3.1 mg/dL	
BUN = 88 mg/dL	
Glucose = 776 mg/dL	
Ketones = positive	

Question 1 Characterize the acid–base disturbance.

Answer Using the Henderson equation, the $[H^+]$ is 32, which corresponds to a pH of 7.48 and close to the patient's pH. From the ABG values, the initial disturbance is respiratory alkalosis, and calculation of secondary response suggests that it is chronic rather than acute respiratory alkalosis. Hyperventilation due to abdominal pain accounts for this acid–base disturbance.

The calculated AG is 43, which is not due to alkalosis, but entirely due to the presence of metabolic acidosis. Insulin withdrawal and subsequent generation of ketoacids (ketones positive) account for this high AG metabolic acidosis.

Assuming the normal AG of 10, this patient has an excess of 33 (43 − 10 = 33; $\Delta AG = 33$) anions. If 1 H^+ is buffered by 1 HCO_3^-, the patient should not have any measurable HCO_3^- in the serum. However, his measured HCO_3^- is 17 mEq/L, suggesting that he had a high level of serum HCO_3^- before the development of metabolic acidosis. Thus, he had metabolic alkalosis prior to the development of metabolic acidosis. This was confirmed by the patient that his vomiting started before he withdrew insulin injections. Thus, the patient has a triple acid–base disorder of *chronic respiratory alkalosis, high AG metabolic acidosis, and metabolic alkalosis*.

Question 2 Does Na^+ need to be corrected for hyperglycemia to calculate AG?

Answer No. From Chap. 4, it is clear that Na^+ correction for hyperglycemia is not needed to calculate the AG.

Question 3 Is $\Delta AG/\Delta HCO_3^-$ useful in the analysis of ABG?

Answer Yes. The $\Delta AG/\Delta HCO_3^-$ ratio >2 is indicative of metabolic alkalosis. In this patient, the $\Delta AG/\Delta HCO_3^-$ ratio is 4.71 ($\Delta AG = 33$; $\Delta HCO_3^- = 7$ (24 − 17); ratio = 33/7 = 4.71). However, it is not necessary to depend on $\Delta AG/\Delta HCO_3^-$ ratio all the time. For example, this patient's serum $[HCO_3^-]$ is disproportionately high compared to the increase in AG, suggesting an underlying metabolic alkalosis.

Case 3 A 31-year-old woman with alcohol abuse and pancreatitis is admitted for shortness of breath, confusion, profuse vomiting, and abdominal pain. She is electively intubated and sedated. The following laboratory results are obtained:

Serum	ABG
Na^+ = 136 mEq/L	pH = 7.01
K^+ = 4.9 mEq/L	pCO_2 = 26 mmHg
Cl^- = 87 mEq/L	pO_2 = 67 mmHg
HCO_3^- = 7 mEq/L	HCO_3^- = 6 mEq/L
Creatinine = 4.1 mg/dL	
BUN = 7 mg/dL	
Glucose = 72 mg/dL	
Ketones = positive	

ABG arterial blood gas, *BUN* blood urea nitrogen

Question 1 Characterize the acid–base disturbance.

Answer Based on low pH and serum [HCO_3^-], and the AG of 42, the patient has a high AG metabolic acidosis due to alcoholic ketoacidosis.

Since the expected pCO_2 for this degree of acidemia is 18.5 mmHg (range 16.5–20.5), the patient has respiratory acidosis (hypercapnia), which is due to the sedative.

As in Case 2, there is a disproportionate relationship between the increase in AG and decrease in HCO_3^-, suggesting an underlying metabolic alkalosis. This is evident from low serum [Cl^-], which is due to vomiting. The $\Delta AG/\Delta HCO_3^-$ ratio is 1.9 ($\Delta AG = 42 - 10 = 32$; $\Delta HCO_3^- = 24 - 7 = 17$; ratio 32/17 = 1.9), which also supports the underlying metabolic alkalosis.

Thus, the acid–base disorder is a *high AG metabolic acidosis, respiratory acidosis, and metabolic alkalosis*.

Question 2 What would be her pH, if her pCO_2 is lowered to 18 mmHg?

Answer Her pH would be ~ 7.18, if her pCO_2 is lowered by increasing the respiratory rate. This pH is obtained by using the Henderson equation:

$$\left[H^+\right] = 24 \times \frac{pCO_2}{HCO_3^-}$$

$$\left[H^+\right] = 24 \times \frac{18}{7} = 62 = pH = 7.18$$

Case 4 A 60-year-old woman with HIV/AIDS is admitted for diarrhea and polysubstance abuse. She is hypotensive (systolic blood pressure of 90 mmHg) with heart rate of 112 beats per minute. Laboratory results are as follows:

Serum	ABG
Na^+ = 130 mEq/L	pH = 7.06
K^+ = 5.5 mEq/L	pCO_2 = 28 mmHg
Cl^- = 112 mEq/L	pO_2 = 84 mmHg
HCO_3^- = 9 mEq/L	HCO_3^- = 8 mEq/L
Creatinine = 1.5 mg/dL	
BUN = 38 mg/dL	
Glucose = 80 mg/dL	
Albumin = 2.3 g/dL	
Urine toxicology: positive for cocaine and heroin	

Question 1 Which one of the following describes the BEST of her acid–base status?

A. Metabolic acidosis and metabolic alkalosis
B. Metabolic alkalosis and respiratory alkalosis
C. Metabolic acidosis and respiratory acidosis
D. Respiratory acidosis, metabolic alkalosis, and metabolic acidosis
E. Metabolic acidosis, respiratory alkalosis, and metabolic alkalosis

The answer is C. The patient has a high AG metabolic acidosis and respiratory acidosis. Her AG is 14 when corrected for normal albumin level of 4.3 g/dL. Note that the AG decreases by 2.5 for each gram decrease in serum albumin from normal values of 4–4.5 g/dL. The superimposed respiratory acidosis is caused by her illicit drug use, which inhibits the medullary respiratory center. The high AG seems to be due to lactic acid production (hypotension) and acute kidney injury.

Question 2 Does $\Delta AG/\Delta HCO_3^-$ ratio have any significance in this patient?

Answer Yes. In diarrhea, the $\Delta AG/\Delta HCO_3^-$ ratio is usually <1 (see Chap. 4). In this patient, this ratio is 0.3 ($\Delta AG = 14 - 10 = 4$; $\Delta HCO_3^- = 24 - 9 = 15$; ratio 4/15 = 0.3). The $\Delta AG/\Delta HCO_3^-$ ratio <1 is suggestive of diarrhea as a cause of abnormal ABG in a patient who does not give adequate history of diarrhea.

Suggested Reading

Adrogué HJ, Madias NE. Respiratory acidosis, respiratory alkalosis, 2 mixed disorders. In: Floege J, Johnson RJ, Feehally J, editors. Comprehensive clinical nephrology. 4th ed. St. Louis: Elsevier/Saunders; 2010. p. 176–89.

Emmett M, Narins RG. Mixed acid–base disorders. In: Narins RG, editor. Maxwell & Kleeman's clinical disorders of fluid and electrolyte metabolism. 5th ed. New York: McGraw-Hill, Inc; 1994. p. 991–1107.

Goodkin DA, Krishna GG, Narins RG. The role of the anion gap in detecting and managing mixed metabolic acid-base disorders. Clin Endocrinol Metab. 1984;13:333–49.

Harrington JT, Cohen JJ, Kassirer JP. Mixed acid-base disturbances. In: Cohen JJ, Kassirer JP, editors. Acid-base. Boston, Little: Brown and Company; 1982. p. 377–90.

Kraut JA, Kurtz I. Mixed acid–base disorders. In: Mount DB, Sayegh MH, Singh AJ, editors. Core concepts in the disorders of fluid, electrolytes and acid–base balance. New York: Springer; 2013. p. 307–26.

Narins RG, Emmett M. Simple and mixed-acid-base disorders. A practical approach. Medicine. 1980:59:161–82.

Rastegar A. Mixed acid–base disorders. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, editors. Acid–base disorders and their treatment. Boca Raton: Taylor & Francis; 2005. p. 681–96.

Walmsley RN, White GH. Mixed acid-base disorders. Clin Chem. 1985;31:321–35.

Chapter 15
Drug-Induced Acid-Base Disorders

In previous chapters, we discussed various systemic and drug-induced causes of acid-base disorders. Since drug-induced acid-base disorders are rather common in daily clinical practice, this chapter summarizes the iatrogenic causes of the four primary acid-base disorders. The pathophysiology of systemic and drug-induced primary acid-base disorders is discussed in their respective chapters.

Metabolic Acidosis

Drugs that cause metabolic acidosis fall into three groups:

1. Drugs that generate endogenous acid (Table 15.1)
2. Drugs that cause loss of HCO_3^- from GI tract or kidney (Table 15.2)
3. Drugs that impair renal tubular function (Tables 15.3, 15.4, and 15.5)

Metabolic Alkalosis

Table 15.6 shows the drugs that cause metabolic alkalosis.

Respiratory Acidosis

Drugs that cause respiratory acidosis are shown in Table 15.7.

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_15

Table 15.1 Common drugs that generate acids with high AG

Drug	Major acid generated	Mechanism
Metformin	Lactic acid	Inhibition of mitochondrial oxidative phosphorylation (mitochondrial dysfunction)
Antiretroviral agents (didanosine, zidovudine, stavudine, zalcitabine, tenofovir, abacavir)	Lactic acid	Mitochondrial dysfunction
Linezolid	Lactic acid	Mitochondrial dysfunction
Propofol	Lactic acid	Mitochondrial dysfunction
Cyanide poisoning	Lactic acid	Mitochondrial dysfunction, hypoxia
Propylene glycol	Lactic acid	Metabolic product
Salicylate	Lactic acid, ketoacid	Mitochondrial dysfunction causing increased lipolysis with ketoacid formation
Ethanol	Ketoacid	Decreased insulin and increased lipolysis, leading to ketoacid formation
Methanol	Formic acid	Metabolic product
Ethylene glycol	Oxalic acid	Metabolic product
Diethylene glycol	2-hydroxy-ethoxyacetic acid	Metabolic product
Toluene	Hippuric acid	Metabolic product
Acetaminophen, netilmicin, flucloxacillin, vigabatrin, paracetamol	Pyroglutamic acid	Dysfunction of γ-glutamyl cycle with reduced glutathione levels
Intravenous diazepam and lorazepam	D-lactic acidosis	Due to propylene glycol used as a solvent
Na/glucose cotransporter 2-inhibitors (dapagliflozin, canagliflozin, empagliflozin)	Ketoacid	Decreased insulin and increased lipolysis, leading to ketoacid formation

Table 15.2 Drugs that cause loss of HCO_3^- from GI tract or kidney with normal AG

Drug	Source of loss	Mechanism
Acetazolamide	Kidney	Inhibition of carbonic anhydrase (CA) in proximal tubule
Topiramate	Kidney	Inhibition of carbonic anhydrase (CA) in proximal tubule
Cholestyramine	GI tract	Adsorption of HCO_3 in exchange for Cl^-, causing hyperchloremic metabolic acidosis
Sevelamer HCl	GI tract	Addition of Cl^-, resulting in hyperchloremic metabolic acidosis
Calcium chloride	GI tract	Loss of HCO_3^- and gain of Cl^-

Table 15.3 Drugs that cause proximal RTA with hypokalemia

Drugs	Mechanism
Acetazolamide, topiramate	Inhibition of carbonic anhydrase in proximal tubule and loss of HCO_3^-
Ifosfamide	Proximal tubule toxicity, cell apoptosis and loss of HCO_3^- (Fanconi syndrome)
Cisplatin, carboplatin, oxaplatin	Proximal tubule toxicity and loss of HCO_3^- (Fanconi syndrome)
Outdated tetracyclines, aminoglycosides	Interfere with mitochondrial function and proximal tubule toxicity (Fanconi syndrome). Gentamicin reduced the conversion of ADP to ATP, thereby reducing the activity of Na/K-ATPase
Valproic acid	Mitochondrial dysfunction
Adefovir, cidofovir, tenofovir	Mitochondrial dysfunction and Fanconi syndrome

Table 15.4 Important drugs that cause distal RTA with hypokalemia

Drug	Mechanism
Amphotericin B	Binds to membrane cholesterol and modifies its permeability in the collecting duct. This altered permeability causes back diffusion of H^+ from tubular lumen to cell
Toluene	Decreases H^+ secretion
Foscarnet	Possible decrease in H^+ secretion
Lithium	Voltage-dependent defect in H^+ secretion and a decrease in H-ATPase activity

Table 15.5 Drugs that cause distal RTA with hyperkalemia

Drugs causing low renin and low aldosterone
NSAIDs
β-blockers
Cyclosporine
Tacrolimus
Drugs causing high renin and low aldosterone
ACE inhibitors
Angiotensin II receptor blockers
Ketoconazole
Heparin
ENaC inhibitors
Amiloride
Trimethoprim
Pentamidine
Triamterene
Na/K-ATPase inhibitors/activation of Na/Cl cotransporter
Cyclosporine
Tacrolimus
Aldosterone blockers
Spironolactone
Eplerenone

Table 15.6 Drugs causing metabolic alkalosis

Drug	Mechanism
Loop diuretics	↑ Delivery of NaCl to cortical collecting duct (CCD), resulting in $\uparrow Na^+$ reabsorption with subsequent ↑ K^+ and H^+ secretion due to loop-diuretic inhibition of Na/K/2Cl cotransporter
Thiazide diuretics	↑ Delivery of NaCl to CCD, resulting in ↑ Na^+ reabsorption with subsequent ↑ K^+ and H^+ secretion due to inhibition of Na/Cl cotransporter
Poorly reabsorbable anions (carbenicillin, other penicillins, phosphate, sulfate)	Delivery of nonreabsorbable anions such as sodium penicillin to the distal tubule promotes K^+ secretion, resulting in hypokalemia and metabolic alkalosis
Gentamicin	Activation of calcium-sensing receptor in the thick ascending limb of Henle's loop, resulting in the development of Bartter-like syndrome
$NaHCO_3$ (baking soda)	Raises serum HCO_3^- level
Sodium citrate, lactate, gluconate, acetate	These anions are metabolized to HCO_3^-
Antacids	Calcium-containing antacids or calcium Ingestion (calcium-alkali syndrome). Hypercalcemia promotes reabsorption of HCO_3^- in the proximal tubule
Licorice, chewing tobacco, carbenoxolone	Cause hypokalemia with subsequent development of metabolic alkalosis
Fludrocortisone	Causes hypokalemia with subsequent development of metabolic alkalosis
Laxatives	Cause hypokalemia with subsequent development of metabolic alkalosis

Table 15.7 Drugs that cause respiratory acidosis

Drug	Mechanism
Anesthetics (diprivan, ketalar, pentothal, etc.)	Depression of medullary respiratory center
Sedatives (pentobarbital, diazepam, clonazepam, etc.)	Depression of medullary respiratory center
Opiates (morphine, codeine, heroin, etc.)	Depression of medullary respiratory center
Succinylcholine	Dysfunction of respiratory muscles
Curare	Dysfunction of respiratory muscles
Aminoglycosides	Neuromuscular blockade

Respiratory Alkalosis

Table 15.8 shows drugs that cause respiratory alkalosis.

Table 15.8 Drugs that cause respiratory alkalosis

Drug	Mechanism
Salicylates	Stimulation of medullary respiratory center
Progesterone	Stimulation of medullary respiratory center
Nicotine	Stimulation of medullary respiratory center
Xanthine derivatives (caffeine, theophylline, pentoxifylline, etc.)	Stimulation of medullary respiratory center
Antipsychotic drug (quetiapine)	Stimulation of medullary respiratory center
Catecholamines	Supraphysiologic doses stimulate medullary respiratory center

Study Questions

Question 1 Match the following drugs with their acid-base disorders

Drug	Acid-base disorder
1. Progesterone	A. Respiratory acidosis
2. Aminoglycosides	B. Respiratory alkalosis
3. Quetiapine	C. High AG metabolic acidosis
4. Licorice	D. Normal AG metabolic acidosis
5. Cyclosporine	E. Metabolic alkalosis
6. Amiloride	F. Distal RTA with hypokalemia
7. Lithium	G. Distal RTA with hyperkalemia
8. Amphotericin B	H. Proximal RTA
9. Cisplatin	
10. Ifosfamide	
11. Acetazolamide	
12. Na/glucose cotransporter 2-inhibitors	

Answers (1) B; (2) A, E, H; (3) B; (4) E; (5) G; (6) G; (7) F; (8) F; (9) H; (10) H; (11) D; (12) C

Question 2 Match the following drugs with their mechanism of action

Drug	Mechanism of action
1. Progesterone	A. Mitochondrial dysfunction
2. Gentamicin	B. Inhibits epithelial sodium channel
3. Quetiapine	C. Activation of calcium-sensing receptor in the thick ascending limb of Henle's loop, resulting in the development of Bartter-like syndrome
4. Licorice	D. Binds to membrane cholesterol and modifies its permeability in the collecting duct. This altered permeability causes back diffusion of H^+ from tubular lumen to cell
5. Metformin	E. Stimulation of medullary respiratory center
6. Amiloride	F. Dysfunction of γ-glutamyl cycle with reduced glutathione levels

Drug	Mechanism of action
7. Propofol	G. Inhibition of carbonic anhydrase
8. Amphotericin B	H. Fanconi syndrome
9. Cisplatin	I. Cause hypokalemia with subsequent development of metabolic alkalosis
10. Ifosfamide	
11. Acetazolamide	
12. Acetaminophen	

Answers (1) E; (2) C; (3) E; (4) I; (5) A; (6) B; (7) A; (8) D; (9) H; (10) H; (11) G; (12) F

Suggested Reading

Brater DG. Drug-induced electrolyte disorders and use of diuretics. In: Kokko JP, Tannen RL, editors. Fluids and electrolytes. Philadelphia: W.B. Saunders Company; 1996. p. 693–728.

Holt CT, Hitchings AW. Drug-induced metabolic acidosis. Adverse Drug React Bull. 2017;304(1):1176–8.

Kitterer D, Schwab M, Dominik M, et al. Drug-induced acid-base disorders. Pediatr Nephrol. 2015;30:1407–23.

Pham AQT, Xu LHR, Moe OW. Drug-induced metabolic acidosis. F1000Res. 2015:1–13.

Wiener SM. Toxicologic acid-base disorders. Emerg Med Clin N Am. 2014;32:149–65.

Wilson KC, Saukkonen JJ. Acute respiratory failure from abused substances. J Intensive Care Med. 2004;19:183–93.

Chapter 16
Acid–Base Disorders in Critically Ill Patients

Acid–base disorders are extremely common in patients admitted to the critical care units because of multiorgan dysfunction. Sepsis, septic shock, toxin ingestion, diabetic ketoacidosis, removal of vomitus by nasogastric suction, massive transfusion with citrated blood, and renal as well as respiratory failure are some of the important causes for acid–base disorders. Hyperchloremic metabolic acidosis is frequently seen due to fluid resuscitation with normal saline or fluids that contain high Cl^-. Among acid–base disorders, some reports suggested metabolic acidosis as the predominant disorder in critically ill patients. For example, an observational cohort study reported that 64% had acute metabolic acidosis. Other studies showed metabolic alkalosis to be the most common acid–base disorder in critically ill patients. Therefore, it is difficult to predict which acid–base disorder predominates in critically ill patients. It should be noted that any acid–base disorder is associated with high morbidity and mortality in critically ill patients. Lindner et al. [1] described an acid–base disorder called hypernatremic alkalosis in critically ill patients. Their study included 51patients who developed hypernatremia (serum Na^+ level > 149 mEq/L) after admission to intensive care units (ICUs). Based on an increase in base excess, hypernatremia was accompanied by an increase in serum HCO_3^- level and pH. The authors suggest that hypernatremic alkalosis should be part of the differential diagnosis of metabolic acid–base disorders. In this chapter, we will discuss the pathophysiology and management of only four primary acid–base disorders (metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis) in critically ill patients.

Metabolic Acidosis

As mentioned above, metabolic acidosis is the most frequently observed acid–base disorder in critically ill patients. Metabolic acidosis develops because of three reasons: (1) renal failure; (2) addition of either endogenous or exogenous anions (H^+);

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_16

Table 16.1 Most common causes of high and normal AG metabolic acidosis in intensive care units

Cause	Unmeasured anions causing high or normal AG
High AG acidosis	
Renal failure Acute kidney injury, uremic acidosis	Sulfate, phosphate, urate
Addition of H^+	
Lactic acid	L-Lactate
Ketoacidosis	Acetoacetate, β-hydroxybutyrate
Methanol	Formate
Ethylene glycol	Gycolate, oxalate
Propylene glycol	L-Lactate
Aspirin	Salicylate, L-lactate, ketoacids
Acetaminophen (Tylenol)	Pyroglutamate (5-oxoproline)
Normal AG acidosis	
Hyperchloremic metabolic acidosis	Cl^- due to normal saline infusion
Acute diarrhea	HCO_3^- due to gastrointestinal loss
Enteric fistulae	HCO_3^- due to gastrointestinal loss
Recovery phase of diabetic ketoacidosis	Loss of ketoacid anions and infusion of Cl^--rich solutions
Cationic amino acids (arginine, lysine, histidine) in parenteral nutrition	H^+ as a metabolic product of these amino acids

and (3) loss of HCO_3^- from the kidney or gastrointestinal tract. As usual, metabolic acidosis is classified into high anion gap (AG) or normal AG groups. Table 16.1 shows the most common causes of metabolic acidosis in critically ill patients.

Selected Conditions of Metabolic Acidosis

L-Lactic acidosis The most extensively studied anion causing high AG metabolic acidosis in critical care units (ICUs) is lactic acid. Indeed, lactic acidosis is the predominant cause of metabolic acidosis in ICUs. As discussed in Chap. 5, type A lactic acidosis is due to hypoxia, but sepsis is probably the most important cause of this acid–base disorder. Measurements of lactate in ICUs are routinely performed, as lactate levels have a prognostic significance. Both absolute levels of lactate and its clearance have been used in various clinical settings as markers of length of stay, severity of shock, morbidity, and mortality. It was shown that patients with septic shock whose initial lactate levels in the Emergency Department were >2 mmol/L had a higher in-hospital mortality rate than those whose levels were 2 or <2 mmol/L. Also, it was shown that lactate levels are associated with proportional increases in mortality rate. One study reported about 70% mortality in critically ill patients with blood lactate levels between 3 and 4 mmol/L.

Increased lactate levels are related to overproduction or decreased clearance by the liver and kidneys. Studies have shown that decreased clearance is associated with higher length of ICU stay and mortality. In a cohort of trauma patients, initial lactate level and its clearance at 6 hours were associated with decreased mortality. In patients with sepsis or septic shock, at least 10% clearance of lactate within 6 hours of presentation has been shown to have a lower mortality rate than those patients with decreased clearance of lactate. Thus, both higher levels and decreased clearance of lactate are associated with higher mortality rate.

Blood lactate levels <5 mmol/L may not have any effect on pH in an individual with serum HCO_3^- level of 24 mEq/L. However, low blood lactate levels in a patient with low HCO_3^- level may have a significant effect on pH. Let us consider the following ABG in a normal subject and critically ill patient.

ABG in normal subject with normal lactate level (1 mmol/L)

pH = 7.40
pCO_2 = 40 mmHg
$[HCO_3^-]$ = 24 mEq/L
pO_2 = 96 mmHg

ABG in a normal subject with 3 mmol/L increase in lactate level is given below (assuming 1 HCO_3^- ion buffers 1 lactate anion (H^+); the resulting HCO_3^- level is 21 mEq/L).

pH = 7.37
pCO_2 = 38 mmHg
$[HCO_3^-]$ = 21 mEq/L
pO_2 = 96 mmHg

Note that this pH of 7.37 will have no significant physiologic change in the body. However, an increase in lactate level of 3 mmol/L will have a profound change in pH and physiologic change in the body.

Initial ABG due to ketoacidosis in a patient with normal lactate level (1 mmol/L).

pH = 7.32
pCO_2 = 30 mmHg
$[HCO_3^-]$ = 15 mEq/L
pO_2 = 92 mmHg

ABG in the presence of 3 mmol/L increase in blood lactate level.

pH = 7.20
pCO_2 = 30
HCO_3^- = 12 (assuming 1 HCO_3^- ion buffers 1 lactate anion (H^+); 15–3 12 mEq/L)
pO_2 = 89 mmHg

Thus, a small increase in blood lactate can have a profound effect on pH in a critically ill patient.

Treatment of lactic acidosis is discussed in Chap. 5, which includes fluid resuscitation, antibiotic use in sepsis, elimination of the cause and judicious use of alkalinizing agents, if required, vasopressors, optimization of O_2 delivery, and renal replacement therapy. Use of $NaHCO_3$ is controversial.

Ketoacidosis Diabetic ketoacidosis rather than starvation or alcohol ketoacidosis is a frequent cause of ICU admission. The pathophysiology and management of diabetic ketoacidosis are discussed in Chap. 6.

Toxin-induced metabolic acidosis Ingestion of methanol, ethylene glycol, and aspirin with electrolyte and acid–base abnormalities requires management in an ICU setting. At times, patients with acetaminophen overdose may present with high AG metabolic acidosis, and these patients may require urine measurements of pyroglutamate (5-oxoproline). The pathophysiology and management of each of these toxin-associated acid–base disorders are discussed in Chap. 7.

Propylene glycol It is a common vehicle for many drugs used in ICUs. It is metabolized to lactic acid by alcohol dehydrogenase. Discontinuation of propylene glycol-containing drugs resolves the high AG metabolic acidosis.

Hyperchloremic metabolic acidosis (HCMA) Of all the causes of HCMA (renal tubular acidosis, renal failure), infusion of large quantities of normal saline during volume resuscitation is the most important cause of this acid–base disorder in ICU patients.

Normal saline contains high Cl^- (154 mEq/L). Recent studies have shown that infusion of solutions containing high Cl^- to critically ill patients has caused not only hyperchloremic metabolic acidosis but also acute kidney injury. Balanced electrolyte solutions with low Cl^- concentration, on the other hand, caused less adverse effects compared to normal saline.

Recovery phase of diabetic ketoacidosis Hyperchloremic metabolic acidosis does develop in some patients in the recovery phase of DKA because the regeneration of HCO_3^- from ketones is decreased due to loss of excess ketones in the urine prior to hospitalization. Also, administration of fluids that contain high chloride may contribute to this type of transient acidosis.

Renal failure Acute kidney injury (AKI) is rather common in ICU patients, and high AG metabolic acidosis develops in most of these patients. AKI superimposed on CKD (chronic kidney disease) is also common. In both AKI and CKD, decreased excretion of H^+ is due to impaired net acid excretion. Details of acid–base disorders in kidney disease are discussed in Chap. 8.

Parenteral nutrition Acid–base disorders of parenteral nutrition are discussed in Chap. 17.

Clinical Manifestations

Metabolic acidosis affects the functions of almost all organ systems. Some of the important clinical manifestations are summarized in Table 16.2.

Management

Identification of the cause or offending agent and starting the appropriate therapy are the initial steps in the management of a patient with metabolic acidosis. The management of various causes of metabolic acidosis was discussed in previous chapters, and only the summary is presented in Table 16.3.

Metabolic Alkalosis

Not only metabolic acidosis but also metabolic alkalosis is rather common in ICUs. Metabolic alkalosis develops when H^+ is removed or HCO_3^- is added to the body. Once metabolic alkalosis develops, it should be maintained. There are several causes that generate and maintain metabolic alkalosis, which are discussed in Chap. 11. The most common causes of metabolic alkalosis are shown in Table 16.4. Additional causes of metabolic alkalosis in non-ICU settings are presented in Chap. 11.

Table 16.2 Clinical manifestations of metabolic acidosis

Cardiovascular
Decreased contractility at pH <7.1
Decreased cardiac responsiveness to catecholamines
Decreased fibrillation threshold
Arterial vasodilation and hypotension
Respiratory
Increased minute ventilation
Dyspnea
Decreased diaphragmatic contractility
Neurologic
Altered mental status
Increased cerebral blood flow
Decreased cerebral metabolism
Others
Decreased anaerobic metabolism
Increased protein catabolism
Increased metabolic rate
Impaired phagocytosis
Decreased ATP production
Impaired skeletal growth

Table 16.3 Management of metabolic acidosis in critically ill patients

Cause	Treatment
High AG acidosis	
Acute kidney injury, uremic acidosis	Renal replacement therapies (RRT) (hemodialysis, CVVHD, CVVHDF)
Lactic acid	Circulatory support with fluids and vasopressors, alkalizing agents ($NaHCO_3$ or THAM, if indicated), thiamine, riboflavin, CVVHD or CVVHDF. Insulin and glucose
Ketoacidosis	Volume replacement, insulin
Methanol	Supportive care (hydration with normal saline), $NaHCO_3$, if indicated, i.v. folinic acid followed by folate, fomepizole, ethanol, if fomepizole not available, RRT if indicated
Ethylene glycol	Same as above except for folinic acid and folate. Thiamine and pyridoxine
Propylene glycol (PA)	Discontinue PA
Aspirin	Circulatory support with hydration, oral activated charcoal, $NaHCO_3$ to alkalinize urine, hemodialysis, if indicated
Acetaminophen (Tylenol)	$NaHCO_3$, hemodialysis
Normal AG acidosis	
Hyperchloremic metabolic acidosis due to NaCl administration	Use balanced solutions
Acute diarrhea	$NaHCO_3$

CVVHD continuous venovenous hemodialysis, *CVVHDF* continuous venovenous hemodiafiltration

Table 16.4 Most common causes of metabolic alkalosis in intensive care units

Chloride-responsive alkalosis
Vomiting
Nasogastric suction
Posthypercapnia
Cl^- depletion alkalosis
Severe hypokalemia
Loop diuretics
Thiazide diuretics
Ringer's lactate
Transfusions
Infusion of $NaHCO_3$
Renal replacement therapies (Hemodialysis, CVVHD, CVVHDF, PD)
Chloride-resistant alkalosis
Hypertensive emergencies
High doses of steroids
Hypercalcemia
Hypoalbuminemia

CVVHD continuous venovenous hemodialysis, *CVVHDF* continuous venovenous hemodiafiltration, *PD* peritoneal dialysis

Discussion of most of the above causes of metabolic alkalosis is discussed in Chap. 11. Renal replacement therapies use dialysate solutions that contain bicarbonate in concentrations above 35 mEq/L and acetate, resulting in metabolic alkalosis not only in acute patients but also in chronic hemodialysis patients.

Selected Conditions of Metabolic Alkalosis

Hypercalcemia It has been shown that hypercalcemia alone can cause metabolic alkalosis. The pathogenesis involves calcium-sensing receptor (CaSR), which is located in the basolateral membrane of the thick ascending limb of loop of Henle (TALH). As discussed in Chap. 2, Na^+ entry into TALH occurs via Na/K/2Cl cotransporter with K^+ reentering into the lumen via K channel. Because of lumen positivity, Ca^{2+} and Mg^{2+} enter the cell through paracellular pathway. CaSR controls this K channel. Hypercalcemia stimulates CaSR, which blocks K channel, and the positive transepithelial potential difference is abolished. As a result, absorption of Na^+, K^+, Cl^-, Ca^{2+}, and Mg^{2+} is inhibited. Hypercalcemia also causes nephrogenic diabetes insipidus with decreased urine concentrating ability. The net result of activation of CaSR by hypercalcemia is loss of water, volume depletion, and loss of above electrolytes. Because of volume depletion, aldosterone activity is increased with further loss of K^+ in the urine. With volume depletion and low PTH levels due to hypercalcemia, HCO_3^- reabsorption in the proximal tubule is enhanced. Loss of Cl^- and enhanced HCO_3^- reabsorption results in metabolic alkalosis, which is sustained by hypokalemia. Metabolic alkalosis improves with hydration, administration of KCl, and lowering serum Ca^{2+} levels.

Drugs such as gentamicin and amikacin also activate CaSR and induce Bartter-like syndrome with hypokalemia, metabolic alkalosis, and diuresis.

Hypoalbuminemia As mentioned in Chap. 3, hypoalbuminemia causes metabolic alkalosis based on the physicochemical evaluation of metabolic acid–base disorders. When plasma protein concentration decreases, the total concentration of weak acids ($[A_{TOT}]$) decreases. This results in decreased $[H^+]$ and an increase in strong ion difference. Based on this concept, McAuliffe et al. [2] presented eight patients with hypoproteinemia and hypoalbuminemia who all had metabolic alkalosis. They had a mean pH of 7.49, HCO_3^- of 31.3 mEq/L, and base excess of +6.9. Their mean total protein and albumin levels were 4.6 g/dL and 2.7 g/dL, respectively. They calculated that for each 1 g decrease in albumin, the standard HCO_3^- increases by 3.4 mEq/L and base excess increases by +3.7 mEq/L. They suggest measurements of plasma protein and albumin concentration with ABG in the analysis of acid–base disorders.

Since most of the critically ill patients have hypoalbuminemia due to poor nutrition and infection/inflammation, the intensivists should take into consideration hypoalbuminemia in the interpretation of acid–base disorders.

It should be noted that hypoalbuminemia is an important factor in the evaluation of AG and the classification of either high AG or non-AG metabolic acidosis for therapeutic considerations. However, the relationship and clinical significance between HCO_3^- and albumin levels in critically ill patients need further evaluation.

Ringer's lactate Infusion of crystalloids containing lactate, acetate, and other anions generates HCO_3^- by metabolism. A healthy individual with normal kidney function can excrete the generated HCO_3^-; however, a critically ill patient with decreased renal function cannot excrete all the generated HCO_3 from large infusions of these solutions. As a result, serum HCO_3^- level increases. Also, some of these solutions contain low Cl^- content. The net result is the development of metabolic alkalosis.

Transfusion Citrate is used as an anticoagulant in stored blood, and citrate is metabolized to HCO_3^-. Each unit of packed red blood cells contains 5 mEq of sodium citrate, and whole blood contains 17 mEq of sodium citrate. During surgery, some patients require massive (>10 units) blood transfusion. These patients with decreased renal function may develop metabolic alkalosis. In addition, relative volume depletion may contribute to the development of alkalemia. Some postoperative patients may have acute hyperventilation, and such patients may have blood pH >7.50 because of superimposed respiratory alkalosis on metabolic alkalosis.

Hypertensive emergencies Hypokalemic metabolic alkalosis is usually observed during hypertensive urgencies. Patients with uncontrolled essential hypertension, renovascular hypertension, primary aldosteronism, and Liddle syndrome occasionally require ICU admission for control of blood pressure. Other forms of hypertension with hypokalemic metabolic alkalosis do not usually require ICU management of their blood pressure.

Clinical Manifestations

The clinical manifestations of metabolic alkalosis are summarized in Table 16.5.

Management

As in metabolic acidosis, identifying the cause and prescribing appropriate therapy are initial steps in the management of metabolic alkalosis. Table 16.6 summarizes treatment of various causes of metabolic alkalosis.

Table 16.5 Clinical manifestations of metabolic alkalosis

Central nervous system
Confusion
Obtundation
Increased excitability
Reduced seizure threshold
Tetany due to hypocalcemia
Cardiovascular
Reduced cardiac and coronary artery blood flow
Arterial vasoconstriction
Increased heart rate
Susceptibility to arrhythmias
Pulmonary
Hypoventilation with hypercapnia
Hypoxia
Metabolic
Hypokalemia
Low ionized Ca^{2+}
Hypomagnesemia
Hypophosphatemia
Increased glycolysis and lactate production

Table 16.6 Management of some causes of metabolic alkalosis in intensive care units

Cause	Treatment
Vomiting	NaCl, KCl
Nasogastric suction	NaCl, KCl
Posthypercapnia	Acetazolamide, HCl, NaCl
Cl^- depletion alkalosis	NaCl
Severe hypokalemia	KCl
Loop diuretics	Discontinue diuretic, KCl, NaCl
Thiazide diuretics	Discontinue diuretic, KCl, NaCl
Renal replacement therapies (hemodialysis, CVVHD, CVVHDF, PD)	Lower HCO_3^- concentration in dialysate
Chloride-resistant alkalosis	
Hypertensive emergencies Primary aldosteronism Renovascular hypertension Liddle syndrome	KCl, K-sparing diuretics (spironolactone, eplerenone, amiloride), surgery, if indicated Angioplasty, surgery, K-sparing Diuretics Amiloride, triamterene
High doses of steroids	Decrease the dose or discontinue the drug
Severe alkalosis and volume overload	Acetazolamide

CVVHD continuous venovenous hemodialysis, *CVVHDF* continuous venovenous hemodiafiltration

Respiratory Acidosis

Respiratory acidosis was discussed in detail in Chap. 12. Only a brief discussion is presented here. In ICUs, both acute and chronic respiratory acidosis are rather common because of various causes, as shown in Tables 16.7 and 16.9. Acute respiratory acidosis results in hypoxemia, and the effects of hypoxemia are more detrimental than hypercapnia and decreased pH. This demands either noninvasive or invasive ventilation.

Clinical Manifestations

Acute respiratory acidosis causes hypoxemia, resulting in several organ dysfunctions.

Among these, central nervous system (CNS) manifestations predominate.

CNS manifestations

- Nausea, vomiting, restlessness, headache, confusion, seizures, and coma.
- Increase in cerebral blood flow due to cerebral vasodilation of capillaries and venules. This cerebral vasodilation is mediated by nitric oxide.

Table 16.7 Causes of acute respiratory acidosis in intensive care unit patients

Depression of medullary respiratory center
Drugs: anesthetics, sedatives, opiates
Cerebral trauma or infarct
Cardiac arrest
Failure of motor functions of respiratory muscles and chest wall
Drugs: succinylcholine, curare, aminoglycosides, fluoroquinolones
Myasthenia gravis crisis
Guillain–Barrè syndrome
Status epilepticus
Airway obstruction
Aspiration
Laryngospasm
Severe bronchospasm
Ventilatory defects
Flail chest
Pneumothorax
Hydrothorax
Adult respiratory distress syndrome
Acute pulmonary embolism
Acute pulmonary edema
Severe asthma
Severe pneumonia
Mechanical ventilation: increased production of CO_2 due to high carbohydrate feedings and fixed minute ventilation

- Hypercapnia increases intracranial pressure due to increased blood volume and increased vascular pressure caused by vasodilation.

Cardiac manifestations
- Increase in blood pressure and heart rate secondary to increased sympathetic tone.
- Increase in both cardiac output and coronary blood flow due to hypercapnia-induced vasodilation.
- Arrhythmias are also common.

Renal effects
- Renal vasodilation with mild hypercapnia and vasoconstriction at pCO_2 >70 mmHg.
- Stimulation of renin–angiotensin II–aldosterone axis due to hypercapnia-induced sympathetic tone. Antidiuretic hormone secretion is also increased.

Management

The following table (Table 16.8) summarizes the management of acute respiratory acidosis. Remember that clinical assessment and proper use of pharmacotherapy are extremely important in the management of acute respiratory acidosis.

Chronic Respiratory Acidosis

Chronic respiratory acidosis, as opposed to acute respiratory acidosis, is well tolerated by most of the patients unless the patient develops acute illness such as pneumonia. There are several causes that can lead to chronic respiratory acidosis, as shown in Table 16.9.

Table 16.8 Management of acute respiratory acidosis

Correct the underlying cause whenever possible
1. Establish a secure patent airway in both awake and obtunded patients
2. Hypercapnic encephalopathy may occur in patients with narcotic overdose
3. Administration of O_2 to improve hypoxemia
4. The aim of O_2 therapy is to achieve pO_2 of 60–70 mmHg or an O_2 saturation >88%
5. Mechanical ventilation is indicated in apneic, obtunded, and hemodynamically unstable patients with pH <7.10 and pCO_2 >80 mmHg. Lowering pCO_2 may be sufficient to raise pH, but $NaHCO_3$ or THAM is needed in some patients
6. Loop diuretics may be needed in a patient with crackles
7. Antibiotics, β_2-agonists, and other bronchodilators, as well as corticosteroids, may be necessary in patients with infection and wheezing to improve ventilation
8. Minimize carbohydrate feedings in ventilator-dependent patients to prevent excess CO_2 generation

Table 16.9 Some causes of chronic respiratory acidosis in intensive care units

Depression of medullary respiratory center
Chronic sedative and opiate addiction
Brain tumors
Failure of motor functions of respiratory muscles and chest wall
Spinal cord injury
Muscular dystrophy
Myxedema
Diaphragmatic paralysis
Airway obstruction
Chronic obstructive pulmonary disease (COPD) (most common cause)
Ventilatory defects
Hydrothorax
Kyphoscoliosis
Interstitial lung fibrosis
Severe chronic pneumonia

Clinical Manifestations

The manifestations of chronic respiratory acidosis are less severe than acute respiratory acidosis because of near normal pH. This is due to renal generation of HCO_3^-, which is estimated at 4 mEq/L for each 10 mmHg increase in pCO_2 above 40 mmHg. Because of this increase in serum HCO_3^-, the pH in chronic hypercapnic patient is maintained around 7.34. Despite near normal pH, the patient may have the following clinical manifestations.

- Hypoxemia associated symptoms such as dyspnea at rest, fatigue, confusion, limited exercise tolerance, and frequent cough are common.
- CNS manifestations include tremors, ataxia, poor appetite, and cerebral vasodilation.
- Cardiovascular effects are pulmonary hypertension (cor pulmonale), peripheral edema, and supraventricular as well as ventricular arrhythmias.

Management

Management of chronic respiratory acidosis is different from that of acute respiratory acidosis. One needs to address the cause of chronic respiratory acidosis and treat appropriately. The primary goal of treatment is to maintain adequate oxygenation as well as alveolar ventilation and amelioration of hypoxemia. Excessive oxygenation should be avoided in order to prevent CNS depression. In addition, the following therapeutic considerations should be continued as necessary:

- Use judiciously sedatives and sleeping pills (when needed) because they depress CNS drive. Avoid long-term use.
- Use judiciously diuretics for lower extremity edema.
- Treat infections. Avoid routine use of antibiotics to prevent infections.
- Continue bronchodilator therapy.
- Recommend appropriate diet to reduce CO_2 production.
- In a patient with severe hypoxemia (arterial $pO_2 < 50$ mmHg), continuous low-flow O_2 therapy may improve pulmonary circulation and gas exchange through reduction in pulmonary vasoconstriction.
- Maintain pO_2 between 60 and 70 mmHg and O_2 saturation of 88–93% with O_2.
- Note that mechanical ventilation is not necessary for a patient who is alert and able to cough and follow medical therapy.
- Obtunded patients and patients with superimposed acute respiratory acidosis may require mechanical ventilation. Minute ventilation should be raised to achieve baseline pH and pCO_2. Sudden drop in pCO_2 may induced posthypercapnic metabolic alkalosis.

Respiratory Alkalosis

Respiratory alkalosis (primary hypocapnia) is characterized by pH >7.45 and pCO_2 <35 mmHg. Hypocapnia results from alveolar hyperventilation due to increased ventilatory drive, which arises from signals originating from lungs, the peripheral chemoreceptors (carotid and aortic), and the central chemoreceptors located in the medullary respiratory center. Respiratory alkalosis can be acute or chronic. With few exceptions, both acute and chronic respiratory alkalosis share common causes.

Acute respiratory alkalosis is frequently observed in ICUs because of several conditions, including anxiety–hyperventilation syndrome, pain, pneumonia, acute asthmatic attack, septicemia, pulmonary embolism, pulmonary edema, salicylate ingestion, or increased minute ventilation in mechanically ventilated patients. Chronic respiratory alkalosis is rather common in patients with central nervous system disorders, interstitial lung diseases, pregnancy, and chronic liver failure. Table 16.10 shows common causes of respiratory alkalosis in ICUs.

Clinical Manifestations

Respiratory alkalosis have CNS, cardiovascular, and metabolic effects, as shown in Table 16.11.

Table 16.10 Causes of respiratory alkalosis in intensive care units

Direct stimulation of medullary respiratory center
Anxiety–hyperventilation syndrome
Stroke
CNS infection, tumor, or trauma
Gram negative sepsis
Liver failure
Pregnancy
Hypermetabolic state (fever, thyrotoxicosis)
Drugs (salicylates, progesterone, nicotine, xanthine derivatives, catecholamines, antipsychotic drug quetiapine)
Pain
Hypoxemic stimulation of medullary respiratory center
Pulmonary diseases (pneumonia, asthma, pulmonary edema, pulmonary embolus, interstitial lung disease, hypotension, severe anemia)
Mechanical ventilation

Table 16.11 Clinical manifestations of respiratory alkalosis

Acute respiratory alkalosis	Chronic respiratory alkalosis
CNS effects	*CNS effects*
Decrease in brain blood flow with a decrease in intracranial and intraocular pressures	Increase in CSF pH
Light-headedness	High CSF lactate, light-headedness may be common
Confusion	*Cardiovascular effects*
Acral paresthesias due to decreased blood flow to the skin	Increase in cardiac output
Cardiovascular effects	Increase in heart rate
Decrease in cardiac output	Normal blood pressure
Coronary vasoconstriction and chest pain	Low plasma volume
Arrhythmias	Reduced blood flow to kidneys and skin
Metabolic effects	*Metabolic effects*
Increase in lactate and ketoacid production	Hyponatremia
Low plasma volume	Hypokalemia
Hyponatremia	Hypophosphatemia
Hypokalemia	Hypocalcemia
Hypophosphatemia	
Hypocalcemia	

Management

Respiratory alkalosis is not benign and no longer self-limited. Treatment is, therefore, warranted. Correction of the primary disorder of respiratory alkalosis is extremely important. Table 16.12 shows the cause-specific treatment of respiratory alkalosis.

Table 16.12 Management of respiratory alkalosis

Cause	Treatment options
Anxiety–hyperventilation syndromes	Rebreathing into a paper or plastic bag, mild sedation, and reassurance
Hypoxia	O_2
Salicylates	Urinary alkalinization, forced diuresis, dialysis
Sepsis	Antibiotics
Asthma	Bronchodilators, corticosteroids
Pneumonia	Antibiotics
Pulmonary edema	Diuretics, improvement in CHF
Pulmonary embolism	O_2, anticoagulation
Cardiac arrhythmias	Lower pH <7.50, acetazolamide, rebreather
Mechanical ventilation	↓ Ventilatory rate and tidal volume, ↑ dead space, mild sedation without skeletal muscle paralysis

Mixed Acid–Base Disorders

Mixed acid–base disorders are frequently encountered in critically ill patients. However, triple acid–base disorders are usually missed unless there is a high index of suspicion. The following table (Table 16.13) shows the clinical setting where double or triple acid–base disorders occur in patients admitted to ICUs. More details of mixed acid–base disorders are presented in Chap. 14.

Study Questions

Question 1 Which one the following primary acid–base disorder is *most* commonly seen in intensive care unit (ICU)?

A. Respiratory alkalosis
B. Respiratory acidosis
C. High AG metabolic acidosis
D. Metabolic alkalosis
E. Respiratory acidosis and metabolic alkalosis

The answer is C. Although any one of the above acid–base disturbance can occur in ICUs, the most likely disturbance is high AG metabolic acidosis due to sepsis, ketoacidosis, and ingestion of toxins. Thus, answer C is correct. Mixed acid–base disorders are also rather common; however, metabolic alkalosis superimposed on respiratory acidosis is usually induced during the management of the patient. In contrast, mixed metabolic acidosis and respiratory alkalosis are rather common.

Table 16.13 Clinical setting of mixed acid–base disorders

Acid–base disorder	Metabolic acidosis and metabolic alkalosis	Metabolic acidosis and respiratory alkalosis	Metabolic acidosis and respiratory acidosis	Metabolic alkalosis and respiratory alkalosis	Metabolic alkalosis and respiratory acidosis	Metabolic acidosis, metabolic alkalosis and respiratory alkalosis	Metabolic acidosis, metabolic alkalosis and respiratory acidosis
Clinical setting	Renal failure (CKD 4 and 5), diabetic ketoacidosis, lactic acidosis with vomiting, or diuretics	Renal failure (CKD 4 and 5) with sepsis, or salicylate intoxication, or pulmonary embolus	Cardiac arrest or renal failure with emphysema, or sedatives, or narcotics	Vomiting, diuretics with pneumonia, or hepatic failure, or pregnancy	Vomiting or diuretics with emphysema, or sedatives	Ketoacidosis with vomiting and abdominal pain, or pneumonia	Ketoacidosis with vomiting, or sedative, or COPD

Question 2 Which one of the following nutrients is implicated in weaning of the patient with impaired lung function MOST difficult?

A. Glutamate
B. Aspartate
C. Essential fatty acids
D. Glucose
E. None of the above

The answer is D. Studies have shown that excess use of glucose-containing solutions or high carbohydrate feeds generate CO_2, which makes weaning of the patient difficult. Thus, answer D is correct. Other nutrients are not involved in generating excess CO_2.

References

1. Linder G, Schwarz C, Grüsing H, et al. Rising serum sodium levels are associated with a concurrent development of metabolic alkalosis in critically ill patients. Intensive Care Med. 2013;39:399–405.
2. McAuliffe JJ, Lind LJ, Leith DE, et al. Hypoproteinemic alkalosis. Am J Med. 1986;81:86–90.

Suggested Reading

Al-Jaghbeer M, Kellum JA. Acid-base disturbances in intensive care patients: etiology, pathophysiology and treatment. Nephrol Dial Transplant. 2015;30:1104–11.
Boyd JH, Walley KR. Is there a role for sodium bicarbonate in treating lactic acidosis in shock? Curr Opin Crit Care. 2008;14:379–83.
Fencl V, Rossing TH. Acid-base disorders in critical care medicine. Ann Rev Med. 1989;40:17–29.
Gunnerson KJ. Clinical review: the meaning of acid-base abnormalities in the intensive care unit-epidemiology. Crit Care. 2005;9:508–16.
Kimmoun A, NovyNovy E, Auchet T, et al. Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside. Crit Care. 2015;19:175.
Kraut JA, Kurtz I. Treatment of acute non-anion gap metabolic acidosis. Clin Kidney J. 2015;8:93–9.
Luke RG, Galla JH. It is chloride depletion alkalosis, not contraction alkalosis. J Am Soc Nephrol. 2012;23:2014–07.
Maehl K, Haug B, Haatten H, et al. Metabolic alkalosis is the most common acid-base disorder in ICU patients. Crit Care. 2014;18:420.
Morgan TJ. Clinical review: the meaning of acid-base abnormalities in the intensive care unit-effects of fluid administration. Crit Care. 2005;9:204–11.
Oh YK. Acid-base disorders in ICU patients. Electrolyte Blood Press. 2010;8:66–71.
Story DA, Poustie S, Bellomo R. Quantitative physical chemistry analysis of acid-base disorders in critically ill patients. Anaesthesia. 2001;58:530–3.
Webster NR, Kulkarni V. Metabolic alkalosis in the critically ill. Crit Rev Clin Lab Sci. 1999;36:497–510.

Chapter 17
Acid-Base Disorders in Liver Disease

The role of the liver in acid-base regulation is often neglected because of the importance given to the lungs and kidneys. This negligence is partly related to few studies of acid-base disorders in liver disease. In Chap. 2, the roles of the lungs and kidneys in acid-base regulation were discussed. In this chapter, a brief discussion on the role of the liver in acid-base balance and its disorders in liver disease is presented. The role of the liver in acid-base balance is divided into four categories:

Role of the Liver in Acid-Base Balance

The liver has the following important roles in maintaining acid-base balance:

1. Lactate metabolism
2. Ketogenesis
3. HCO_3^- and NH_4^+ metabolism
4. Albumin synthesis

Lactate metabolism The body generates approximately 1300 mmol of lactate (Chap. 5) and an equal number of H^+ daily. These H ions titrate tissue and blood HCO_3^- so that the pH is maintained at normal level. Lactate is removed mostly in the liver (above 722 mmol) by gluconeogenesis to glucose and by oxidation to CO_2 and water. Both processes generate HCO_3^-, which buffers acids produced during normal life, such as exercise or other activities. In this way, the liver functions as a regulatory organ in acid-base balance. If gluconeogenesis is impaired, lactate accumulates, and metabolic acidosis develops. Also, lactic acidosis develops due to excess production and/or decreased removal from the liver. In these cases, addressing the cause for lactic acidosis improves patient care.

Ketogenesis Another source of H^+ and HCO_3^- is inadequate oxidation of fatty acids and formation of ketone bodies, namely, acetoacetic acid and β-hydroxybutyric

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_17

acid (Chap. 6). In the fed state, only small concentrations of ketones are formed. However, large quantities are formed in conditions such as starvation, insulin deficiency, and alcohol use even in the presence of normal liver. Following correction of these conditions, the ketones are oxidized to CO_2 and water. Thus, the liver regulates metabolism of ketones.

HCO_3^- and NH_4^+ metabolism Another major function of the liver is disposal of HCO_3^- formed from amino acids from protein diet. Approximately 1000 mmol each of HCO_3^- and NH_4^+ are formed from 100 g protein intake, assuming that the protein diet contains only neutral amino acids. This huge load of HCO_3^- must be consumed; otherwise, as a buffer, it may have tremendous effect on acid-base balance. Such high amounts of both HCO_3^- and NH_4^+ cannot be excreted by the kidneys because of limitation in urine production. The major pathway for elimination (consumption) of these two products is their utilization in hepatic urea synthesis. The liver is the only organ that generates urea via urea cycle enzymes. The generated urea is subsequently excreted in the urine. Urea is generated according to the following equation:

$$2HCO_3^- + 2NH_4^+ \rightarrow \text{Urea} + CO_2 + 3H_2O$$

or

$$2HCO_3^- + 2NH_4^+ \rightarrow \text{Urea} + CO_2 + H_2O + 2H^+$$

In the above equation, HCO_3^- and NH_4^+ are consumed in the same stoichiometry as they are produced during protein breakdown. Thus, consumption or detoxification of NH_4^+ occurs during urea genesis. Note that for each mol of urea synthesized, 2 mol of H^+ are produced. This H^+ eventually titrates HCO_3^-.

Both urea and glutamine synthesis occur at two different hepatocytes located in the liver: (1) periportal hepatocytes located at the inflow of the sinusoidal bed and (2) perivenous hepatocyte at the acinar outflow. The first hepatocyte contains urea cycle enzymes where urea is synthesized, and the second hepatocyte contains glutamine synthetase where glutamine is synthetized. Glutamine synthesis has a high affinity for NH_4^+; therefore, it acts as a scavenger for the NH_3 that escaped periportal urea synthesis in the first hepatocyte. Thus, NH_4^+ is detoxified by these two mechanisms, namely, urea and glutamine synthesis. Figure 17.1 shows schematically the formation of urea in periportal hepatocyte and glutamine synthesis in perivenous hepatocyte.

The importance of the liver in the regulation of acid-base balance is explained during metabolic acidosis or alkalosis. Whenever acidosis occurs, the liver responds with a decrease in urea synthesis. As a result, HCO_3^- is retained and subsequently used to correct acidosis. It is estimated that a 10% decrease in urea synthesis retains approximately 100 mEq of HCO_3^- per day. NH_4^+ that is formed during protein catabolism is taken up by the perivenous hepatocyte and used for glutamine synthesis. Thus, when urea synthesis is switched off during acidosis to conserve HCO_3^-, glutamine synthesis is increased, and this glutamine serves as a nontoxic transport

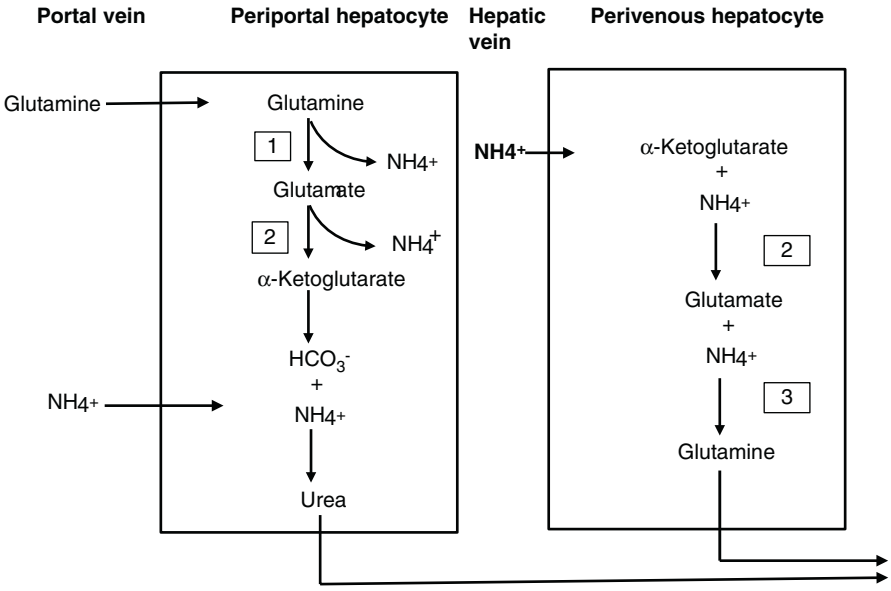

Fig. 17.1 Synthesis of urea and glutamine in hepatocytes. (1) Represents phosphate-dependent glutaminase; (2) represents glutamate dehydrogenase; and (3) represents glutamine synthetase. Both urea and glutamine are taken up by the kidney

form of NH_3 to the kidney. In the kidney, renal ammoniagenesis increases to help in the excretion of excess H^+ generated during metabolic acidosis. In this way, the liver and kidney participate in maintaining acid-base balance during metabolic acidosis. Several other factors, which are not discussed here, also contribute to the decrease in urea synthesis during metabolic acidosis.

Conversely, during metabolic alkalosis, the HCO_3^- produced from protein catabolism does not aggravate alkalosis. This is related to enhanced urea synthesis. As a result, both HCO_3^- and NH_4^+ are used up, and their amount decreases. Furthermore, degradation of glutamine increases with a supply of NH_4^+ for more urea synthesis. Thus, increased urea synthesis consumes HCO_3^- during metabolic alkalosis.

Hypoalbuminemia The liver is the major organ for albumin synthesis. As expected, albumin synthesis is decreased in liver failure. This results in a decrease in total weak acid concentration and an increase in strong ion difference, causing metabolic alkalosis (Chap. 3). Thus, hypoalbuminemia causes metabolic alkalosis. It has been reported that for each gram/dL decrease in albumin from normal, base excess increases by 3.7 mEq/L. This acid-base disorder may not be that significant in a normal individual, but it may have some significance in critically ill patients with severe metabolic acidosis by slightly increasing the pH.

From the above discussion, it is clear that the liver plays an important role in acid-base regulation besides the lungs and kidneys. Let us now discuss the various types of acid-base disorders in liver disease.

Acid-Base Disorders in Liver Disease

Several acid-base disorders have been described in patients with liver disease. Respiratory alkalosis is the predominant acid-base disturbance in patients with liver disease. The incidence and degree of respiratory alkalosis varied with severity of liver disease. For example, about 61% of patients with fulminant hepatic failure had respiratory alkalosis. In patients with stable chronic cirrhosis, the percentage varied from 25% to 83%. However, respiratory alkalosis was documented in 72–86% in patients with hepatic coma. In some of these patients, the reported arterial pH was >7.50. Similarly, the incidence of metabolic alkalosis varied from study to study with percentages from 0% to 36%.

Metabolic acidosis is not that common compared to alkalosis. High AG metabolic acidosis is rather common in patients with acute-on-chronic liver failure than in patients with stable chronic liver disease. In these acute-on-chronic liver failure patients, lactic acidosis and unmeasured anions accounted for high AG metabolic acidosis. Also, concomitant respiratory alkalosis was present with high AG metabolic acidosis. Arterial pH <7.10 was associated with 100% mortality. In addition to high AG metabolic acidosis, non-AG metabolic acidosis (renal tubular acidosis) has been reported in patients with autoimmune hepatitis. Patients with alcoholic hepatitis seem to develop incomplete renal tubular acidosis.

Mixed acid-base disturbances are also commonly observed in liver disease, particularly in those with chronic severe decompensated liver disease. Indeed such mixed acid-base disturbances were reported in 11 of 14 studies reviewed. Combined respiratory and metabolic alkalosis with hypokalemia is a frequently seen acid-base disturbance in patients with liver disease. Mixed respiratory alkalosis and metabolic acidosis are seen particularly in patients with ketoacidosis or toxic alcohol ingestion. Respiratory acidosis is rather uncommon but is an expected acid-base disturbance in patients with respiratory muscle fatigue due to hypokalemia and hypophosphatemia. Let us discuss briefly each one of these acid-base disorders that occur in liver disease.

Respiratory Alkalosis

As mentioned above, respiratory alkalosis seems to be the major acid-base disorder observed in patients with liver disease. It results from hyperventilation due to stimulation of respiratory center. Pathophysiology of respiratory alkalosis includes (1) hypoxia due to pulmonary ventilation-perfusion defects; (2) increased NH_3 levels; (3) increased progesterone levels; (4) ascites with elevated diaphragm with pleural effusions; (5) sepsis; and (6) catecholamines. Despite systemic alkalosis, intracellular acidosis occurs in the brainstem of patients with liver disease. Furthermore, alkalosis increases brain and liver NH_3 uptake. Both these processes enhance hyperventilation.

One must be cautious in lowering blood pH acutely in patients with hepatic encephalopathy. Studies have shown that lowering pH by administration of acet-

azolamide or 5% CO_2 inhalation caused further deterioration in neurologic status despite normal systemic NH_3 level. This suggests that care should be taken to lower systemic pH in patients with hepatic encephalopathy.

Metabolic Alkalosis

Metabolic alkalosis has been observed from 0% to 36% of patients with liver disease. However, it is the belief of many acid-base physiologists that metabolic alkalosis is rather uncommon in liver disease unless the patients are treated with diuretics, or taking antacids, or received blood transfusions with citrate as an anticoagulant.

In this connection, the reader is remained of the role of the liver in acid-base balance. A normal liver can handle approximately 1000 mmol of HCO_3^- daily in the process of urea synthesis. In fulminant hepatic failure or in severe decompensated liver disease, urea synthesis is decreased with underutilization of HCO_3^- and resultant metabolic alkalosis. However, this mechanism for metabolic alkalosis is disputed. Another mechanism is hypoalbuminemia-induced metabolic alkalosis. Again the clinical significance of hypoalbuminemia-induced metabolic alkalosis is disputed.

Hypophosphatemia and hypokalemia from poor oral intake and respiratory alkalosis may contribute to the development of metabolic alkalosis. Thus, decreased urea synthesis, hypoalbuminemia, hypophosphatemia, and hypokalemia should be considered in the evaluation of metabolic alkalosis in a patient with liver disease in the absence of diuretics or vomiting.

Hyperaldosteronism, which is common in liver disease, alone may not induce metabolic alkalosis because of reduced delivery of Na^+ to the cortical collecting duct. However, aldosterone can elicit its action once a thiazide or loop diuretic can deliver Na^+, which is reabsorbed in exchange for K^+ and H^+.

High Anion Gap (AG) Metabolic Acidosis

Metabolic acidosis is less common than metabolic alkalosis. It has been reported that metabolic acidosis occurs in 10–15% of patients at later stages of liver disease. Although the liver is the major organ for lactate disposal, lactate does not accumulate unless a stable cirrhotic patient develops sudden deterioration in liver disease (acute-on-chronic liver failure), sepsis (systemic or spontaneous bacterial peritonitis), and shock due to gastrointestinal bleeding, alcoholic ketoacidosis, or metformin use. Under these conditions, lactic acid accumulates with resultant high AG metabolic acidosis. In a prospective study of 181 patients with cirrhosis, high AG metabolic acidosis developed due to sepsis, gastrointestinal bleeding, acute kidney injury, and hepatic encephalopathy. Lactic acid and unmeasured anions accounted for metabolic acidosis. Mortality was high in these patients with pH<7.06.

The low incidence of metabolic acidosis in cirrhotic patients is partly attributed to the failure to recognize its presence when physiologic approach for acid-base analysis was followed. This was emphasized in a study by Funk et al. [1]. These investigators evaluated acid-base status in 50 stable cirrhotic patients and 10 healthy controls and analyzed acid-base status by physicochemical method of Stewart (Chap. 3). Pertinent labs in control and cirrhotic (Child-Pugh B and C) patients:

Labs	Control	Patient
Na^+ (mEq/L)	140	133
Cl^- (mEq/L)	102	105
HCO_3^- (mEq/L)	23.5	22.2
Albumin (g/dL)	4.43	2.79
pH	7.42	7.45
pCO_2	37.1	31.9
AG	14.5	9.9 (corrected for albumin of 4.43 g/dL)
Base excess (BE, mEq/L)	1.1	−1.0
BE_{Alb}	0.1	4.6
BE_{Na}	0.0	−2.1
BE_{Cl}	0.8	−2.3
BE_{UMA}	−0.1	−0.7

UMA unmeasured anions

Based on the above lab data, the authors interpreted the acid-base disorder as follows:

1. Respiratory alkalosis (predominant disorder)
2. Metabolic alkalosis due to hypoalbuminemia, as evidenced by increased BE_{Allb}
3. Dilutional acidosis due to water excess, as evidenced by decreased BE_{Na}
4. Hyperchloremic metabolic acidosis, as evidenced by decreased BE_{Cl}
5. Metabolic acidosis due to unmeasured anions (decreased BE_{UMA})

Although actual Cl^- is normal (100 mEq/L) in patients, corrected Cl^- for dilution is increased (105 mEq/L), suggesting the presence of hyperchloremic metabolic acidosis. Metabolic acid-base disorder in these patients is not clinically apparent because hypoalbuminemic alkalosis, hyperchloremic metabolic acidosis, and dilutional acidosis offset each other with resultant normal metabolic acid-base state.

Please note that the physiologic approach reveals only chronic respiratory alkalosis despite correction of AG for albumin. Thus, evaluation of acid-base disorders in liver disease requires both physiologic and physicochemical approaches.

Normal Anion Gap (AG) Metabolic Acidosis

Normal AG (hyperchloremic) metabolic acidosis in liver disease results from three important causes: (1) diarrhea, (2) renal tubular acidosis (RTA), and (3) medications. Table 17.1 shows various causes of normal AG metabolic acidosis.

Table 17.1 Causes of normal AG metabolic acidosis in liver disease

1. *Diarrhea*
Lactulose
2. *Renal tubular acidosis*
A. Liver disease
Chronic active hepatitis
Biliary cirrhosis
Alcoholic liver disease
Hepatoma
B. Diseases involving both the liver and kidney
Wilson's disease
Amyloidosis
Galactosemia
Gycogen storage diseases
Cystinosis
3. *Medications*
Spironolactone
Amiloride
Triamterene
Cholestyramine
Acetazolamide

Diarrhea

Diarrhea in patients with liver disease is commonly related to infections, bile salts, and lactulose administration. Loss of HCO_3^- in the stool results in metabolic acidosis. AG is normal owing to a proportionate increase in serum Cl^- to maintain electroneutrality. Lactulose is frequently used in patients with liver disease to reduce the production of NH_3 and improve hepatic encephalopathy. Diarrhea is induced by lactulose with resultant mild hyperchloremic metabolic acidosis.

Renal Tubular Acidosis (RTA)

An association between liver disease and RTA has been suggested as early as 1943. As shown in Table 17.1, chronic active hepatitis, primary biliary cirrhosis, and patients with hepatoma have inability to acidify their urine. Distal RTA has been reported in these conditions. In a large study, 32% of patients with chronic liver disease were found to have distal RTA. Renal biopsies in patients with chronic hepatitis and biliary cirrhosis have shown tubulointerstitial disease as a possible mechanism for tubular dysfunction in these patients. Additional studies have shown that hypergammaglobulinemia is another mechanism for distal tubular dysfunction in patients with chronic hepatitis and biliary cirrhosis. Nephrolithiasis, a complication of distal RTA, is seen in some of these patients (see Chap. 8).

In patients with Wilson's disease, amyloidosis, galactosemia, glycogen storage disease, and cystinosis have both hepatic and proximal tubular dysfunction. As a result, HCO_3^- loss in the urine with propionate increase in serum Cl^- results in hyperchloremic metabolic acidosis.

In alcoholic liver cirrhosis, systemic acidosis is not present but becomes evident following an oral acid load with calcium chloride. In this study, the patients were unable to acidify their urine below pH 5.58. This inability to acidify the urine was subsequently shown by several studies. These patients with alcoholic liver cirrhosis were classified as having incomplete RTA. Decreased Na^+ delivery to the distal tubule for exchange with H^+ seems to be the mechanism for the underlying acidification defect in these patients. As no disturbances in electrolyte abnormalities are seen, treatment for incomplete RTA is not necessary.

Medications

K^+-sparing diuretics (spironolactone, amiloride, triamterene) can cause hyperchloremic metabolic acidosis with mild hyperkalemia in patients with severe liver disease.

Cholestyramine is a nonabsorbable anion exchange resin that serves as a bile acid sequestrant. It is used in the treatment of hypercholesterolemia, pruritus due to biliary obstruction, and elevated bile acid levels. This resin adsorbs HCO_3^- and releases Cl^-. As a result, hyperchloremic metabolic acidosis develops.

Use of carbonic anhydrase inhibitors such as acetazolamide for glaucoma causes hyperchloremic metabolic acidosis in patients with liver disease.

Thus, patients with chronic liver can develop hyperchloremic metabolic acidosis due to diarrhea, proximal, distal, and incomplete RTA as well as medications.

Respiratory Acidosis

Respiratory acidosis is rather uncommon compared to other types of acid-base disorders. It occurs in patients with massive ascites, elevated diaphragm, and pulmonary atelectasis. It also occurs in patients with suppressed respiratory center due to narcotics. Fatigue of intercostal muscle due to hypokalemia and hypophosphatemia results in hypercapnia and respiratory acidosis.

Study Questions

Case 1 A 36-year-old man with cirrhosis is admitted for management of hepatic encephalopathy. Arterial blood gas (ABG) shows the following values:

pH = 7.45.
pO_2 = 90 mmHg.
pCO_2 = 26 mmHg.
Serum HCO_3^- = 18 mEq/L.

Question 1 What is the acid-base disorder in this patient?

A. Metabolic acidosis
B. Respiratory acidosis
C. Metabolic alkalosis
D. Respiratory alkalosis
E. Respiratory alkalosis and metabolic acidosis

The answer is D. The ABG values suggest only chronic respiratory alkalosis with appropriate secondary physiologic response (compensation). Metabolic alkalosis is unlikely because of low HCO_3^- concentration. Both pH and HCO_3^- levels do not suggest respiratory acidosis. This is not a mixed acid-base disturbance because of appropriate renal compensation. Thus, answer D is correct.

Case 2 A 40-year-old woman with cirrhosis is admitted for management of ascites. She is on 200 mg of spironolactone daily. Which one of the following acid-base disturbance is MOST likely in this patient?

A. Respiratory alkalosis and high anion gap (AG) acidosis
B. Respiratory alkalosis and normal AG acidosis
C. Respiratory alkalosis and metabolic alkalosis
D. Respiratory alkalosis only
E. Metabolic alkalosis only

The answer is B. A patient with cirrhosis and ascites usually has respiratory alkalosis because of hyperventilation. Spironolactone causes hyperchloremic (non-AG) metabolic acidosis. Unless the patient has sepsis or hypoxia or other conditions that cause acid production, metabolic acidosis is uncommon in cirrhotic patients. Patients on loop diuretics for management of ascites usually develop metabolic alkalosis superimposed on respiratory alkalosis. Single acid-base disturbance is present only in uncomplicated cirrhotic patient. Thus, answer B is correct.

Case 3 A 46-year-old malnourished woman with cirrhosis and ascites undergoes large volume paracentesis as an outpatient. Four days later she comes to the Emergency Department (ED) with complaints of nausea, vomiting, abdominal pain, and dizziness. In ED, she is found to have hypotension with orthostatic blood pressure and pulse changes. Labs and ABG show:

Serum chemistry	ABG
Na^+ = 140 mEq/L	pH = 7.36
K^+ = 5.4 mEq/L	pO_2 = 84 mmHg
Cl^- = 102 mEq/L	pCO_2 = 25 mmHg
HCO_3^- = 14 mEq/L	HCO_3^- = 13 mEq/L
Creatinine 4.4 mg/dL	
Albumin = 3.2 g/dL	

Question 1 Which one of the following BEST characterizes the acid-base disturbance in this patient?

A. High anion gap (AG) acidosis and respiratory alkalosis
B. Respiratory alkalosis and normal AG acidosis
C. Respiratory alkalosis and metabolic alkalosis
D. Respiratory alkalosis only
E. Metabolic acidosis only

The answer is A. The patient has a high AG metabolic acidosis due to acute kidney injury (AKI) precipitated by large volume paracentesis without albumin infusion. Albumin corrected AG is 26.5, which is high for renal failure alone. The secondary response (compensation) for metabolic acidosis is respiratory with low pCO_2. The expected pCO_2 is 29 mmHg (27–31 mmHg). However, the patient's pCO_2 is 25, suggesting that respiratory alkalosis is superimposed on metabolic acidosis. Thus, answer A is correct.

As noted above, AKI alone will not give an AG of 26.5. Usually AKI will give an AG of 18, and the difference between 26.5 and 18 is 8.5. This difference in AG may be due to other anions such as lactic acid, ketoacids, or other anions. Based on hypotension and relative hypoxemia on ABG, lactic acidosis and uremic acidosis seem responsible for this high AG. Indeed, serum lactate levels were 9 mmol/L. Other answers are incorrect.

References

1. Funk G, Doberer D, Osterreicher C, et al. Equilibrium of acidifying and alkalinizing metabolic acid-base disorders in cirrhosis. Liver Int. 2005;25:205–12.

Suggested Reading

Ahya SN, Soler MJ, Levitsky J, Battle D. Acid-base and potassium disorders in liver disease. Sem Nephrol. 2006;26:466–70.

Atkinson DE, Bourke E. The role of urea genesis in pH homeostasis. Trends Biochem Sci. 1984;9:297–300.

Bernardi M, Predieri S. Editorial. Disturbance of acid-base balance in cirrhosis: a neglected issue warranting further insights. Liver Int. 2005;25:463–6.

Cohen RD. Roles of the liver and kidney in acid-base regulation and its disorders. Br J Anaesthesia. 1991;67:154–64.

Drol A, Horvatits T, Roedl K, et al. Acid-base status and its clinical implications in critically ill patients with cirrhosis, acute-on-chronic liver failure and without liver disease. Ann Intensive Care. 2018;8:48.

Golding PL. Renal tubular acidosis in chronic liver disease. Postgrad Med J. 1975;51:550–6.

Guder WG. Renal and hepatic nitrogen metabolism in systemic acid base regulation. J Clin Chem Clin Biochem. 1987;23:457–66.

Häussinger D. Glutamine metabolism in the liver: overview and current concepts. Metabolism. 1989;38(Suppl 1):14–7.

Häussinger D, Gerok W, Sies H. Hepatic role in pH regulation: role of the intracellular glutamine cycle. Trends Biochem Sci. 1984;9:300–2.

Oster JR, Perez GO. Acid-base disturbances in liver disease. J Hepatol. 1986;2:299–306.

Record CO, Iles RA, Cohen RD, et al. Acid-base and metabolic disturbances in fulminant hepatic failure. Gut. 1975;16:144–9.

Scheiner B, Lindner G, Reiberger T, et al. Acid-base disorders in liver disease. J Hepatol. 2017;67:1062–73.

Chapter 18
Acid-Base Disorders in Total Parenteral Nutrition

Patients undergoing total parenteral nutrition (TPN) have several underlying systemic illnesses such as infection, surgical operations, cachexia, malnutrition, and malfunctioning gastrointestinal tract. Therefore, these patients are subject to both acidotic and alkalotic conditions. In addition, the composition of TPN solutions such as amino acids and glucose can predispose them to these acid-base disturbances. Let us discuss each one of the four primary acid-base disorders in detail.

Metabolic Acidosis

Hyperchloremic metabolic acidosis was rather common with infusion of older TPN solutions because they contained protein hydrolysates and certain synthetic amino acids (lysine, arginine, and histidine) that were infused in hydrochloride form. In newer TPN preparations, arginine and histidine are available as free base and lysine as lysine acetate. Thus, the incidence of metabolic acidosis is greatly reduced.

Metabolic acidosis, when present, is mostly related to the presence of amino acids.

TPN solutions contain cationic (lysine, arginine, and histidine), anionic (aspartate and glutamate), and sulfur-containing (methionine, cysteine, and cystine) amino acids. Cationic amino acids contain nitrogen in their side chains, and when metabolized, they generate H^+ at the rate of 1 mol per 1 mol of amino acid. Metabolism of sulfur-containing amino acids yields 2 mol of H^+ (from sulfuric acid) per 1 mol of amino acid. Aspartate and glutamate have carboxylic (COO^-) groups in their side chain, and when metabolized, they consume H^+ with resultant formation of HCO_3^-. Thus, these amino acids reduce acid load (H^+ load) to the body. H^+ that are produced from cationic and sulfur-containing amino acids are generally excreted as net acid excretion in the urine. If the patient has renal dysfunction, these H^+ are retained,

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_18

causing high anion gap metabolic acidosis. Management of this acid-base disorder involves $NaHCO_3$ and renal replacement therapy in patients with renal dysfunction.

Occasionally, hyperchloremic metabolic acidosis develops due to high Cl^- content in TPN solution. This will improve with lowering of Cl^- and increasing acetate in TPN solution. In patients with diarrhea and renal tubular acidosis, TPN may exacerbate hyperchloremic metabolic acidosis, and appropriate management of these disorders will correct this acid-base disorder.

Patients who are severely deficient in thiamine develop lactic acidosis despite TPN, which includes vitamins. This is related partly to the presence of high glucose in TPN solutions that demands thiamine for pyruvate dehydrogenase activity and partly loss of thiamine in the urine due to hyperosmolality-induced osmotic diuresis. Although it is a rare occurrence, monitoring thiamine levels may be necessary in some patients. Also, biotin deficiency has been reported to cause lactic acidosis. Replacement of both thiamine and biotin to maintain normal levels prevents the development of lactic acidosis.

Hypophosphatemia is common in patients on TPN despite its inclusion in these solutions. The reason for hypophosphatemia is cellular shift caused by glucose and amino acid-induced insulin secretion. In insulin-resistant diabetic subjects, insulin growth factor-1 transports phosphate into the cell. Hypophosphatemia decreases net acid excretion with resultant retention of H^+ and development of metabolic acidosis.

Metabolic Alkalosis

Metabolic alkalosis is frequently seen in patients on TPN. Both the underlying disease processes requiring nasogastric suction, duodenal obstruction causing vomiting, and excess acetate infusions can increase serum HCO_3^- level with resultant metabolic alkalosis. Also, osmotic diuresis-induced volume depletion can raise serum HCO_3^- level and causes metabolic alkalosis. Dialysis patients on TPN develop post-dialysis metabolic alkalosis due to bicarbonate-containing dialysis solutions.

Respiratory Acidosis

TPN solutions contain glucose (carbohydrate), fatty acids (fats), and amino acids (protein). Respiratory quotient (RQ) is calculated for these nutrients to evaluate the basal metabolic rate of these nutrients. RQ is calculated from ratio of CO_2 production to O_2 consumption by the body. The RQ values for carbohydrates, fats, and proteins are 1.0, 0.7, and 0.8, respectively. When RQ value exceeds 1.0 for high carbohydrate intake, CO_2 production is high. In TPN, glucose content is usually high; as a result, the production of CO_2 is high. Patients with normal lung function

can eliminate this excess CO_2, and CO_2 balance is maintained. If patients have impaired lung function (COPD or other diseases), they cannot eliminate this excess CO_2. As a result they retain CO_2 and develop respiratory acidosis. TPN-induced hypercapnia has been known for a long time. In addition to hypercapnia, infusion of large quantities of glucose was found to increase O_2 consumption, energy expenditure, tidal volume, and respiratory rate.

One of the earliest studies reported acute respiratory failure in three patients on ventilator support within 12 h following administration of high carbohydrate load.

Both CO_2 production and RQ increased with the development of respiratory acidosis. In one patient, pCO_2 increased from 43 to 93 mmHg, and pH fell from 7.40 to 7.25 within 24 h after increasing caloric intake from 1500 to 2500 kcal/day. Thus, high carbohydrate (glucose) load in TPN can cause respiratory acidosis in patients with impaired lung function.

Herve et al. [1] studied gas exchange and arterial blood gases in six patients with chronic respiratory failure, who were ventilated at low (6 L/min) and high (10 L/min) minute ventilation during three randomized nutritional regimens: (1) control (255 kcal/day); (2) glucose TPN (2550 kcal/day); and (3) lipid TPN (3000 kcal/day). At both levels of ventilation, TPN solutions increased CO_2 production and arterial pCO_2 when compared to controls. At low minute ventilation, both CO_2 production and hypercapnia were much less in those on lipid TPN than those on glucose TPN. These investigators suggest that the risk of TPN-induced hypercapnia is lower, if minute ventilation is increased before the start of TPN.

In summary, TPN induces respiratory acidosis in patients with impaired respiratory function, and weaning these patients from ventilators is difficult if they are on high glucose TPN feedings. Weaning is less difficult if they are on lipid TPN feedings or low caloric intake from carbohydrates.

Respiratory Alkalosis

Primary respiratory alkalosis has not been reported in patients with impaired lung function who are on TPN. It should be, however, noted that high glucose and amino acids in TPN may stimulate respiratory rate and lower serum HCO_3^- concentration.

Study Questions

Case 1 A 52-year-old man underwent abdominal surgery for intestinal perforation complicated by sepsis, requiring intubation. Two weeks later, he was started on TPN with 10% glucose. Which one of the following complications results from glucose TPN?

A. Hypercapnia
B. Increased O_2 consumption

C. Increased tidal volume
D. Increased respiratory rate
E. All of the above

The answer is E. TPN-induced hypercapnia has been known for a long time. In addition, infusion of large quantities of glucose was found to increase O_2 consumption, energy expenditure, tidal volume, and respiratory rate. Thus, answer E is correct.

Question 1 Current TPN solutions contain several classes of amino acids. Which one of the following amino acids generates H^+ following their metabolism during TPN administration?

A. Aspartate and glutamate
B. Methionine, cysteine, and cystine
C. Lysine, arginine, and histidine
D. B and C
E. All of the above

The answer is D. Newer TPN solutions contain cationic (lysine, arginine, and histidine), anionic (aspartate and glutamate), and sulfur-containing (methionine, cysteine, and cystine) amino acids. When cationic amino acids are metabolized, H^+ are generated at the rate of 1 mol per 1 mol of amino acid. Metabolism of sulfur-containing amino acids yields 2 mol of H^+ per 1 mol of amino acid. On the other hand, metabolism of anionic amino acids consumes H^+ with generation of HCO_3^-. Thus, oxidation of aspartate and glutamate, which are anionic amino acids, reduces acid load to the body. Thus, answer D is correct.

Question 2 Which one of the following is an important cause of metabolic alkalosis in patients on TPN?

A. Vomiting and gastric suction
B. Lysine acetate
C. Volume depletion due to osmotic diuresis
D. All of the above
E. A only

The answer is D. Metabolic alkalosis is not uncommon in patients on TPN. Both the underlying disease processes requiring nasogastric suction, duodenal obstruction causing vomiting, and excess acetate infusions can increase serum HCO_3^- level with resultant metabolic alkalosis. Also, osmotic diuresis-induced volume depletion can raise serum HCO_3^- level and causes metabolic alkalosis. Thus, answer D is correct.

References

1. Herve P, Simonneau G, Girard P, et al. Hypercapnic acidosis induced by nutrition in mechanically ventilated patients: glucose versus fat. Crit Care Med. 1985;13:537–40.

Suggested Reading

Askanazi J, Nordenstrom J, Rosenbaum SH, et al. Nutrition for the patient with respiratory failure. Anesthesiology. 1981;54:373–6.

Covellli HD, Black JW, Olsen MS, et al. Respiratory failure precipitated by high carbohydrate loas. Ann Intern Med. 1981;95:579–81.

Dark DS, Pingleton SK, Kerby GR. Hypercapnia during weaning. A complication of nutritional support. Chest. 1986;88:141–3.

Dounousi E, Zikou X, Koulouras V, et al. Metabolic acidosis during parenteral nutrition: pathophysiological mechanisms. Indian J Crit Care Med. 2015;19:270–4.

Iacone R, Scanzano C, D'Isanto A, et al. Prediction of renal acid load in adult patients on parenteral nutrition. Pharmaceutics. 2018;10:43.

Jones BJM, Chopra P, Groning J, et al. Acid-base disturbance during home parenteral nutrition-An observational cohort study. E-SPEN Eur e-J Clin Nutr Metab. 2011;6:e31–5.

Knochel JP. Complications of total parenteral nutrition. Kidney Int. 1985;27:489–96.

Kushner RF. Total parenteral nutrition-associated metabolic acidosis. J Parenter Enter Nutr. 1986;10:306–10.

Sugiura S-I, Inagaki K, Noda Y, et al. Acid-load during total parenteral nutrition: comparison of hydrochloric acid and acetic acid on plasma acid-base balance. Nutrition. 2000;16:260–3.

Chapter 19
Acid-Base Disorders in Pregnancy

During pregnancy, several anatomic and physiologic changes occur in pulmonary system. Pertinent lung volume changes in pregnancy are summarized in Table 19.1.

Acid-Base Disorders

Acid-base values in the mother and fetus are important to assess fetal oxygenation and fetal well-being in utero. Respiratory alkalosis is commonly observed in pregnancy, whereas metabolic alkalosis is rather uncommon. Metabolic acidosis and respiratory acidosis are also uncommon. Let us discuss each of these disturbances in detail.

Respiratory Alkalosis

Among the four primary acid-base disorders, the most common acid-base disorder is respiratory alkalosis. As early as 1912, investigators observed hyperventilation, low pCO_2, and HCO_3^- concentrations in pregnancy. In subsequent years, similar values were reported in several studies. In these later studies, blood pH was reported to be >7.40. Based on alkaline pH, low pCO_2, and low HCO_3^-, the primary acid-base disturbance was found to be respiratory alkalosis. Table 19.2 shows various arterial blood gas (ABG) values in early and late pregnancy and at high altitude. It takes at least 1 week after delivery to return these abnormal ABG values to nonpregnant values.

As discussed in Chap. 13, increased levels of progesterone stimulate the medullary respiratory center to cause hyperventilation and respiratory alkalosis. Also, increased minute ventilation decreases pCO_2 levels. Elevation of diaphragm due to growing fetus may also cause hyperventilation and lower pCO_2. Respiratory

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_19

Table 19.1 Lung volume changes in pregnancy

O_2 consumption	↑ (20%). Further increase during labor and delivery
Minute ventilation	↑ (30–50%)
Tidal volume	↑ (40–50%)
Functional residual capacity	↓ (20%)
Total lung capacity	↓ (4–5%) or no change
Vital capacity	No change
Respiratory rate	No change, but hyperventilation is common

Table 19.2 Acid-base values in pregnancy at sea level and high altitude

Measurement	Nonpregnant	1st trimester	3rd trimester	1388 meters	4200 meters
pH	7.35–7.45 (7.40)	7.40–7.44 (7.42)	7.41–7.45 (7.43)	7.43–7.49 (7.46)	7.39–7.52 (7.43)
pO_2 (mmHg)	80–100 (90)	99–111 (105)	100–112 (106)	84–98 (91)	48–76 (61)
pCO_2 (mmHg)	35–45 (40)	27–32 (28)	23–29 (26)	24–28 (26)	14–32 (24)
HCO_3^- (mEq/L)	22–26 (24)	17–19 (18)	15–19 (17)	17–18 (18)	12–20 (16)
O_2 saturation (%)	94–100 (98)	98	98	96	90

Adapted from several sources; see Suggested Reading
() mean

alkalosis moves the oxyhemoglobin dissociation curve rightward, thereby releasing O_2 to the periphery and facilitating its transfer to the placenta. Maternal O_2 increases from normal 98 to 101–106 mmHg because of increased minute ventilation, and this increased pressure facilitates transplacental transfer. Changing from supine to sitting position increases pO_2 by approximately 13 mmHg. When maternal pO_2 falls below 70 mmHg, fetal oxygenation decreases substantially.

Diffusion of CO_2 occurs rapidly between maternal and fetal circulations. The lower maternal pCO_2 favors diffusion of CO_2 from the fetus to the maternal circulation for excretion.

Respiratory alkalosis does not need any treatment during pregnancy, as hyperventilation and biochemical abnormalities of ABG values return to normal following delivery.

Metabolic Acidosis

Pregnancy per se does not cause primary metabolic acidosis. However, metabolic acidosis does occur as a result of starvation due to persistent vomiting, diabetic ketoacidosis, lactic acidosis, or ingestion of alcohols. Occasionally,

further lowering of serum HCO_3^- with normal pH has been observed in some pregnant women.

Metabolic Alkalosis

Primary metabolic alkalosis alone is rather uncommon during pregnancy because respiratory alkalosis is common in normal pregnancy. A few cases of metabolic alkalosis have been reported. The major reason is severe nausea and vomiting (hyperemesis gravidarum). Thus, metabolic alkalosis is superimposed on respiratory alkalosis. Conditions that predispose to this mixed acid-base disorder include continuation of diuretics for hypertension, Bartter syndrome, Gitelman syndrome, Liddle syndrome, licorice ingestion, antacids, and pica such as baking soda. There are other common conditions, as discussed in Chap. 11, that may induce metabolic alkalosis. It should be noted that women who seek medical attention rather late following a few days of severe vomiting may develop starvation ketosis. In such cases, it is not uncommon to see a triple acid-base disturbance (respiratory alkalosis, metabolic alkalosis, and high anion gap metabolic acidosis).

Treatment includes prevention of vomiting and administration of normal saline, which improves pH, Cl^-, and HCO_3^-. Cautious use of proton pump inhibitors may improve metabolic alkalosis.

Respiratory Acidosis

Primary respiratory acidosis in pregnancy has not been reported. It may be seen in women opiate overdose, COPD (chronic obstructive pulmonary disease), or severe asthma.

Study Questions

Question 1 Which one of the following acid-base disorders is MOST likely during pregnancy?

A. High anion gap (AG) metabolic acidosis
B. Metabolic alkalosis
C. Respiratory alkalosis
D. Respiratory acidosis
E. Metabolic acidosis and metabolic alkalosis

The answer is C. Respiratory alkalosis is the most common acid-base disorder in pregnancy because of increased progesterone levels, which stimulate medullary respiratory center. Also, increased minute ventilation decreases pCO_2 levels. Thus, answer C is correct.

Metabolic acidosis is not that common unless the patient develops diabetic or starvation ketosis. Metabolic alkalosis is also uncommon unless the patient has vomiting or hyperemesis gravidarum. Metabolic alkalosis is usually superimposed on respiratory alkalosis. Respiratory acidosis is extremely rare.

Question 2 Which one of the following strategies for managing respiratory alkalosis is APPROPRIATE in pregnancy?

A. Opiates to suppress respiratory rate
B. A rebreather (Ambu bag)
C. $NaHCO_3$
D. No treatment
E. Delivery

The answer is D. Respiratory alkalosis is self-limited in uncomplicated pregnancy, which improves following delivery at the end of gestation. Therefore, no treatment is needed. Other treatment modalities are not necessary. Thus, answer D is correct.

Suggested Reading

Alkhasoneh M, Jacobs J, Kaur G. A case of severe metabolic acidosis during pregnancy. Clin Case Rep. 2019;7:550–2.

Bobrowski RA. Pulmonary physiology in pregnancy. Clin Obste Gynecol. 2010;53:285–300.

Hankins GDV, Clark SL, Harvey CJ, et al. Third trimester arterial blood gas and acid-base values in normal pregnancy at moderate altitude. Obstet Gynecol. 1996;88:347–50.

Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med. 2011;32:1–13.

Hui L, Shuying L. Acute starvation ketoacidosis in pregnancy with severe hypertriglyceridemia. Medicine. 2018;97(19):e0609.

Frise C, Noori M, Williamson C. Severe metabolic alkalosis in pregnancy. Obstret Med. 2013;6:138–40.

Liberatore SM, Pistelli R, Patalano F, et al. Respiratory function during pregnancy. Respiration. 1984;46:145–50.

Myers VC, Muntwyler E, Bill AH. The acid-base balance disturbance of pregnancy. J Biol Chem. 1931;98:253–60.

Omo-Aghoja L. Maternal and fetal acid-base chemistry: a major determinant of perinatal outcome. Ann Med Health Sci Res. 2014;4:8–17.

MacRae DJ, Palavradh D. Maternal acid-base changes in pregnancy. J Obstet Gynaecol Br Commonw. 1967;74:11–6.

McAulifffe F, Kametas N, Krampl E, et al. Blood gases in pregnancy at sea level and at high altitude. BJOG. 2001;108:980–5.

Seeger H, Salfeld P, Eisel R, et al. Completed pregnancies in inherited distal renal tubular acidosis: importance of acid-base balance. J Nephrol. 2017;30:455–60.
Sjöstedt S. Acid-base balance of arterial blood during pregnancy, at delivery and in the puerperium. Am J Obstet Gynecol. 1962;84:775–9.
Sobrevilla LA, Cassinelli MT, Carcelen A, et al. Human fetal and maternal oxygen tension and acid-base status during delivery at high altitude. Am J Obstet Gynecol. 1971;111:1111–8.
Weinberger SE, Weiss ST, Cohen WR. Pregnancy and the lung. Am Rev Respir Dis. 1980;121:559–77.

Chapter 20
Acid-Base Disorders in Surgical Patients

Acid-base disorders are rather common in surgical patients. These disorders occur in perioperative (preoperative, intraoperative, and postoperative) periods. Disturbances in all four primary acid-base balances have been reported in surgical patients. However, these disturbances are less severe in healthy patients undergoing elective surgery compared to those who undergo emergent surgery.

Acid-Base Disorders During Preoperative Surgery

Although uncommon in a healthy subject, asymptomatic metabolic acidosis may be seen in individuals who have such diseases as diabetic ketoacidosis, diabetics with type IV RTA, chronic kidney disease stages 3 and 3A, and chronic diarrhea. Use of certain medications such as spironolactone, ACE-inhibitors, cholestyramine, and antiretroviral agents (see Chap. 15) may present with mild metabolic acidosis. Also, vigorous hydration prior to surgery may cause hyperchloremic acidosis. Interestingly, one study found metabolic acidosis in 17% of patients with elective major surgery prior to incision, which was attributed to fasting and infusion of normal saline. Thus, acid-base disorders during preoperative period are related to the patient's pre-existing disease and other conditions, as shown in Table 20.1.

Metabolic alkalosis is commonly observed in patients on loop or thiazide diuretics for hypertension or edema. Patients who go for gastric outlet obstruction surgery may have metabolic alkalosis due to vomiting. Patients with COPD may have chronic respiratory acidosis. Respiratory alkalosis is seen infrequently unless the patient is anxious about the impending surgery.

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2_20

Table 20.1 Pertinent causes of metabolic acidosis during preoperative surgery

High AG acidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Lactic acidosis
Uremic acidosis
Normal AG acidosis
Hyperchloremic metabolic acidosis due to saline
Chronic diarrhea
Loss of alkali from gastrointestinal fistulas and drainages
Ureterosigmoidostomy
Ileal loop bladder
Renal tubular acidosis
Acetazolamide
ACE-inhibitors
Antiretroviral agents
Type IV RTA due to diabetes and hypertension

Acid-Base Disorders During Intraoperative Surgery

Intraoperative development of acid-base disorders, particularly lactic acidosis and hyperchloremic metabolic acidosis, is rather common. Tissue hypoperfusion and cellular hypoxemia are important causes of lactic acidosis, while administration of normal saline is the cause for hyperchloremic metabolic acidosis. During surgery, loss of HCO_3^- occurs because pancreas is not stimulated in surgical crisis. Third-spacing of intestinal fluids causes hypovolemia, which requires volume replacement. Usually normal saline is used which causes hyperchloremic metabolic acidosis. This type of acidosis has been demonstrated in noncardiac and nonvascular surgery patients who underwent intraoperative procedures for more than 4 h. Increase in intraabdominal pressure during laparoscopic cholecystectomy seems to cause lactic acidosis, and low pressure pneumoperitoneum (6–8 mmHg) attenuates lactic acidosis. During liver transplantation surgery, lactic acid accumulates due to decreased hepatic clearance, low cardiac output-induced hypoperfusion, and intraoperative blood loss. Thus, lactic acidosis and hyperchloremic metabolic acidosis are the predominant acid-base disorders during intraoperative period. Mild metabolic alkalosis can occur during certain intraabdominal surgeries as a result of fluid sequestration into peritoneum and intestinal lumen, causing hypovolemia and increase in serum HCO_3^- concentration. Respiratory acid-base disturbances are uncommon with good oxygenation and mechanical ventilation.

Acid-Base Disorders During Postoperative Surgery

Anion gap (AG) metabolic acidosis and non-AG metabolic acidosis are commonly seen during immediate postoperative period. Actually these acid-base disorders are carried on from intraoperative period because of lactic acid production and

administration of normal saline. Metabolic alkalosis is infrequent, unless the patient received citrated blood during intraoperative procedure. Citrate is metabolized to HCO_3^-, and if the kidneys are unable to excrete excess HCO_3^-, metabolic alkalosis develops. Vomiting and nasogastric suction may also lead to metabolic alkalosis. Hydration with normal saline usually improves metabolic alkalosis. Respiratory acidosis can develop postoperatively in patients with normal lungs due to inadequate ventilation. Also, excessive sedation with narcotics for pain can cause respiratory acidosis. Rarely upper abdominal or thoracic surgery can cause respiratory alkalosis due to shallow breathing by the patient.

Administration of $NaHCO_3$ can improve metabolic acidosis in well-oxygenated patients. NaCl or other balanced crystalloids may be necessary to improve hypovolemia and associated metabolic alkalosis. Respiratory acid-base disorders can be managed by appropriate ventilator settings.

Study Questions

Case 1 A 50-year-old woman had abdominal surgery for intestinal perforation. Postoperatively she received opiates for abdominal pain. Which one of the following primary acid-base disturbances is MOST likely to be present in the patient?

A. Metabolic acidosis
B. Metabolic alkalosis
C. Respiratory acidosis
D. Respiratory alkalosis
E. Respiratory acidosis and respiratory alkalosis

The answer is C. Opiates inhibit medullary respiratory center. As a result, hypercapnia develops, leading to respiratory acidosis. Thus, answer C is correct.

Case 2 An 18-year-old man is admitted for observation following motor vehicle accident. He is kept NPO (nothing per mouth) for series of imaging studies and is receiving half-normal saline. He gave the history of driving whole night without food intake other than black coffee. Following 16 h waiting for the tests, serum chemistry shows bicarbonate of 18 mEq/L. Venous pH is 7.39. Respiratory rate is 12 per min. Which one of the following primary acid-base disturbances is MOST likely in this patient?

A. Respiratory alkalosis
B. Metabolic acidosis
C. Metabolic alkalosis
D. Respiratory acidosis
E. Metabolic acidosis and metabolic alkalosis

The answer is B. The reason for low bicarbonate is probably starvation ketosis because the patient has not been eating for more than 24 h. The simple and best test is urinalysis, which may show the presence of ketones. It is not unusual to see an

elderly developing starvation ketosis awaiting surgery or imaging studies in a busy hospital with trauma center.

Chronic respiratory alkalosis also lowers serum HCO_3^- level to this level, but time to develop chronicity is >2–3 days. Also, this patient's respiratory rate is normal. Therefore, respiratory alkalosis is unlikely. Serum HCO_3^- concentration is >24 mEq/L in both metabolic alkalosis and respiratory acidosis. In combined metabolic acidosis and metabolic alkalosis, serum HCO_3^- concentration is usually within normal limits. Thus, all the other answers are incorrect.

Question 1 Which one of the following acid accumulations causes metabolic acidosis during intraoperative surgery?

A. Acetoacetic acid
B. β-Hydroxybutyric acid
C. Hippuric acid
D. Lactic acid
E. None of the above

The answer is D. Lactic acidosis is the most likely acid generated during intraoperative period because of hypotension, hemorrhage, hypoxia, etc. Thus, answer D is correct. Other acid production is unlikely.

Suggested Reading

Carson SAA, Morris LE, Edmark KW, et al. Acid-base management for open-heart surgery. 1964;XXIX:456–66.
Clark J, Walker WF. Acid-base problems in surgery. World J Surg. 1983;7:590–8.
Ibraheim OA, Samarkandi AH, Alshery H, et al. Lactate and acid base changes during laparoscopic cholecystectomy. Middle East J Anaesthesiol. 2006;18:757–68.
Lawton TO, Quinn A, Fletcher SJ. Perioperative metabolic acidosis: The Bradford Anaesthetic Department Acidosis Study. J Intens Care Soc. 2019;20:11–7.
Mark NH, Leung JM, Arieff AI, et al. Safety of low-dose intraoperative bicarbonate therapy: a prospective, double-blind, randomized study.The study of perioperative ischemia (SPI) research group. Crit Care Med. 1993;21:959–65.
Mateveev GP, Vabishchevich AV, Kiseleva EA. Acid-base disturbances during liver transplantation. Anesteziol Reanimatol. 2012:48–51.
Mostert M, Bonavia A. Starvation ketoacidosis as a cause of unexplained metabolic acidosis in the perioperative period. Am J Case Rep. 2016;17:755–8.
Park CM, Chun HK, Jeon K, et al. Factors related to post-operative metabolic acidosis following major abdominal surgery. ANZ J Surg. 2014;84:574–80.
Sealy WC, Young WG, Hickam JB. Postoperative acidosis. AMA Arch Surg. 1957;75:57–60.
St Clair JW, Wong ML. Ileal neobladder: An important cause of nonanion gap metabolic acidosis. J Emerg Med. 2017;52:e179–82.
Waters JH, Miller LR, Clack S, et al. Cause of metabolic acidosis in prolonged surgery. Crit Care Med. 1999;27:2142–6.

Index

A
Acetyl-CoA, 87
Acid-base balance
  ABG
    arterial vs. venous blood sample for, 4
    factors, 5, 6
  HCO_3^-, 3
  liver disease, 281
    HCO_3^- and NH_4^+ metabolism, 282, 283
    hypoalbuminemia, 283
    ketogenesis, 281
    lactate metabolism, 281
  normal ABG values, 3
  pCO_2, 3
  pH, 2
  pO_2, 3
  primary acid–base disorders, 4
  secondary physiologic response, 5
Acid-base disorder, 39, 263
  ABG, evaluation, 39
  acute respiratory acidosis, 47, 48
  acute respiratory alkalosis, 49, 50
  anion gap, 22–24, 41
    $\Delta AG/\Delta HCO_3^-$, use of, 44, 45
    clinical use of, 42
    high AG metabolic acidosis, mnemonic for, 42
    hyperglycemia and, 42, 43
    normal AG metabolic acidosis, 43, 44
    normal AG values, 42
    normal values, 42
  approach to patient, 50, 51
  base excess method, 24–27
  chronic respiratory acidosis, 49
  chronic respiratory alkalosis, 50, 51
  in critically Ill patients
    chronic respiratory acidosis, 273–275
    metabolic acidosis, 263–268
    metabolic alkalosis, 267, 269–271
    mixed acid-base disorders, 277, 278
    respiratory acidosis, 272, 273
    respiratory alkalosis, 275, 276
  evaluation, 52, 53
  Henderson–Hasselbalch, 40, 41
  hydration and acid–base disorders-induced changes, 55–61
  during intraoperative surgery, 306
  in gastrointestinal diseases (*see* Gastrointestinal diseases)
  in kidney disease (*see* Kidney disease)
  in liver disease (*see* liver disease)
  metabolic acidosis, 46, 47
  metabolic alkalosis, 46–48
  mixed, evaluation, 53–55
  pathogenesis and clinical manifestations, 46
  pCO_2, 29
  physicochemical methods, 28, 29, 34–36
  physiologic methods, 21, 22, 27, 34–36
  during postoperative surgery, 306, 307
  in pregnancy (*see* Pregnancy)
  during preoperative surgery, 305, 306
  primary disturbances and secondary response, 39
  secondary physiologic response, 45, 46
  SID, 30, 31
  Stewart's classification, 31–34
  terminology, 40
  TPN (*see* Total parenteral nutrition (TPN))
  trans-atlantic acid-base debate, 28
  weak acids, total concentration, 31

© Springer Nature Switzerland AG 2020

A. S. Reddi, *Acid-Base Disorders*, https://doi.org/10.1007/978-3-030-28895-2

Acid–base disturbance, 200, 203
Acidemia, 40
Acidosis, 40
  correction of, 168
  DKA, 93, 94
Acute exacerbation, 240
Acute kidney injury (AKI), 122, 171, 290
Acute respiratory acidosis, 27, 47, 48, 218, 219, 227
  acute severe asthma, 220
  antibiotics, 221
  cardiac manifestations, 219, 221
  chronic respiratory acidosis, superimposed on, 220
  CNS manifestations, 221
  diagnosis, 221, 222
  increased CO_2 production, 220
  neuromuscular disorders, 220
  opiates, 220
  renal effects, 221
  treatment, 222, 223
Acute respiratory alkalosis, 49, 50, 233
  anxiety-hyperventilation syndrome, 234
  clinical manifestations, 236, 237
  CNS diseases, 235
  drugs, 235
  high altitude, 234, 235
  liver disease, 236
  pregnancy, 236
  pulmonary diseases, 236
  sepsis, 236
Acyl-CoA, 87
Alcohol abuse, 253–255
Alcoholic ketoacidosis, DKA and, 97
  clinical manifestations, 99
  laboratory findings, 99
  pathogenesis, 98
  treatment, 99, 100
Alkalemia, 40, 199
Alkalosis, 40
Alveolar ventilation, 216, 217
Amiloride, 207
Ammonia, 16–19
Anion gap (AG), 22–24, 41, 306
  $\Delta AG/\Delta HCO_3^-$, use of, 44, 45
  clinical use of, 42
  high AG metabolic acidosis, mnemonic for, 42
  hyperglycemia and, 42, 43
  low AG metabolic acidosis and low serum albumin correction, 43, 44
  normal AG metabolic acidosis, 43
  normal AG values, 42
  normal values, 42
Antiretroviral agents, lactic acidosis, 70
Apparent mineralocorticoid excess syndrome (AME), 191
Arterial blood gas (ABG), 1, 40, 289
  arterial vs. venous blood sample for, 4
  technique, 1, 2
Autosomal recessive proximal RTA, 134

B
Bartter syndrome, 190, 208, 211
Base excess method, 1, 24–27
Bicarbonate
  generation of, 11, 15–19
  handling in, 160
  reabsorption, regulation of, 14, 15
Bilevel positive airway pressure (BPAP), 224
Biliary fistulas, 165
Blood gas analyzer (BGA), 1
Bronchodilators, 229
Buffer(s), 9, 10
Buffer base, 24

C
Calcium-alkali syndrome, 193
Carbonic anhydrase inhibitors, 288
Carnitine, 86
Carnitine palmitoyl transferase 1 (CPT1), 86
Central chemoreceptors, 214
Chemoreceptors, 214
Cholestyramine, 166, 288
Chloride Cl^-, intestinal secretion of, 159, 160
Chronic kidney disease (CKD), 171, 172, 180
  dietary acid load, reduction of, 176, 177
  dietary consumptions, 182
  metabolic acidosis, adverse effects, 174, 175
  metabolic acidosis, pathophysiology of, 173, 174
  NAE, 173
  $NaHCO_3$/sodium citrate, use of, 174, 175
  pattern of acid-base disorders, 173
  treatment, 174
Chronic metabolic acidosis, complications, 180
Chronic obstructive pulmonary disease (COPD), 59, 60, 226, 229, 230, 241
Chronic respiratory acidosis, 27, 49, 218, 223
  clinical manifestations, 224, 225
  COPD, 224
  critically Ill patients, 273

management, 274, 275
manifestations, 274
diagnosis, 223, 225
OHS, 224
PAHS, 224
treatment, 225, 226
Chronic respiratory alkalosis, 50, 51, 233, 308
anxiety-hyperventilation syndrome, 234
clinical manifestations, 237, 238
Cirrhosis, 290
CKD, 180
c-Myc, 68
Collecting duct, 13, 14
Colon, Na^+ and Cl^- transport in, 159
Congenital chloridorrhea, 195
Congestive heart failure (CHF), 58, 59
Continuous positive airway pressure (CPAP), 224
Continuous veno-venous hemofiltration (CVVH), 80
Contraction alkalosis, 32
Cystic fibrosis, 193

D
Dent disease, 136
Diabetes
type 1, 252, 253
type 2, 58, 59, 152
Diabetic ketoacidosis (DKA), 85, 86
alcoholic ketoacidosis and, 97
clinical manifestations, 99
laboratory findings, 99
pathogenesis, 98
treatment, 99, 100
clinical manifestations, 90
electrolyte deficit, correction of, 92, 93
euglycemic, 95
HHS and, 95
clinical manifestations, 95, 96
definition, 95
elctrolytes, 97
fluids, 97
insulin, 97
laboratory findings, 95
pathogenesis, 96
precipitating factor, 96
precipitating factors, 97
treatment, 97
hyperglycemia, 86
hyperglycemia and acidosis, correction of, 93, 94
ketogenesis, 86–88
ketonemia and ketonuria, 89
laboratory findings, 90, 91
metabolic acidosis, 88
precipitating factors, 89
precipitating factors, identification and treatment of, 94
recovery phase of, 266
starvation ketoacidosis and, 100
treatment, 90, 91, 94
volume deficit, correction of, 91, 92
Diarrhea, 166
acid–base disorders, types of, 163, 164
diagnosis, 162, 163
liver disease, 287
treatment, 164, 165
types of, 162
water and electrolyte loss, 161, 162
Dichloroacetate, 74
Dietary acid load, reduction of, 176, 177
Diethylene glycol (DEG), 111, 124
clinical manifestations, 113
diagnosis, 113
metabolism, 112
treatment, 113
Dilutional acidosis, 32
Distal renal tubular acidosis (RTA), 181
Distal RTA, 127, 148, 151, 154, 181
with hyperkalemia, 142
causes, 143
diagnosis, 144, 145
treatment, 145
Distal tubule, 12, 14
D-lactic acidosis, 75
acute toxicity, 77, 78
clinical manifestations, 76
diagnosis, 76
long-term management, 78
pathogenesis, 77
toxicity, 76
treatment, 77
Drug abuse, 149
Drug-induced acid-base disorders, 257
metabolic acidosis, 257–259
metabolic alkalosis, 257, 260
respiratory acidosis, 257, 261

E
Electrolyte, 169
Electrolyte deficit, correction of, 92
Electrolyte loss, 161
Encephalopathy, 77
Endogenous acids, 7, 8

Endogenous base, 8
Ethylene glycol (EG), 109
  clinical manifestations, 109, 110
  diagnosis, 110, 111
  metabolism, 109
  treatment, 111
Euglycemic DKA, 95

F
Familial hyperaldosteronism type 1, 209
Filtered $HCO3^-$, reabsorption of, 11
Flucloxacillin, 125
Fomepizole, 107, 123, 124
Formic acid, 106, 123

G
Gastrointestinal diseases
  biliary and pancreatic fistulas, 165
  cholestyramine, 166
  diarrhea
    acid–base disorders, types of, 163, 164
    diagnosis, 162, 163
    treatment, 164, 165
    types of, 162
    water and electrolyte loss, 161, 162
  intestinal electrolyte transport
    Cl^-, intestinal secretion of, 159, 160
    colon, HCO_3^- handling in, 160
    colon, Na^+ and Cl^- transport in, 159
    GI fluids, volume and electrolyte concentrations of, 161
    small intestine, Na^+ and Cl^- transport in, 157–159
  laxative abuse, 166
  urinary-intestinal diversions, 165, 166
  villous adenoma, 165
  water handling, 157
Gastrointestinal fluids, volume and electrolyte concentrations of, 161
Gastrointestinal mechanisms
  congenital chloridorrhea, 195
  laxative abuse, 195, 196
  villous adenoma, 195
  vomiting and nasogastric suction, 194, 195
Gitelman syndrome, 190, 206, 208, 211
Glucocorticoid-remediable hyperaldosteronism (GRA), 191, 209
Glucose, 279
Glutathione, 117
Glycolic acid, 109

H
Headache, 202
Hemodialysis (HD), 107, 108, 177, 178
Hemodynamic stability, 100
Henderson equation, 199, 226
Henderson–Hasselbalch equation, 9, 23, 40, 41
Henle's loop, 12
Hepatic encephalopathy, 289
Highly active antiretroviral therapy (HAART), 168
Hydration, 55, 56
Hydrochlorothiazide (HCTZ), 210, 229
Hyperbicarbonatemia, 40
Hypercalcemia, 193, 269
Hypercapnia, 40, 217
Hyperchloremic metabolic acidosis (HCMA), 32, 152, 163, 167, 248, 263, 266
Hyperglycemia, 42, 43, 86, 93, 94
Hyperglycemic hyperosmolar state (HHS), and DKA, 95
  clinical manifestations, 95, 96
  definition, 95
  elctrolytes, 97
  fluids, 97
  insulin, 97
  laboratory findings, 95
  pathogenesis, 96
  precipitating factor, 96
  precipitating factors, 97
  treatment, 97
Hyperkalemia, 142–146, 153
Hyperlactatemia, 65–67, 69
Hypernatremia, 209
Hypernatremic alkalosis, 263
Hypertensive emergencies, 270
Hyperventilation, 52
Hypoalbuminemia, 269, 270, 283
Hypoaldosteronism, type 4 RTA with, 150
Hypobicarbonatemia, 40
Hypocalcemia, 93
Hypocalciuria, 191
Hypocapnia, 40, 231
Hypokalemia, 140, 168, 200
Hypomagnesemia, 93
Hyponatremic hypertensive syndrome, 209, 210
Hypophosphatemia, 294
Hyporeninemic hypoaldosteronism, 153
Hypotension, 81
Hypothyroidism, 210
Hypoxia, 81

Hypoxia-inducible transcription factor-1 (HIF-1), 68

I
Incomplete renal tubular acidosis, 142
Insulin, 74, 93
Interstitium, 25
Intestinal electrolyte transport
  Cl^-, intestinal secretion of, 159, 160
  colon
    $HCO3^-$ handling in, 160
    Na^+ and Cl^- transport in, 159
  GI fluids, volume and electrolyte concentrations of, 161
  small intestine, Na^+ and Cl^- transport in, 157–159
Intestinal perforation, 295
Intraoperative surgery, acid-base disorders during, 306
Isopropyl alcohol, 114, 115, 124
Isosmotic, 158

K
Ketoacidosis, 266
Ketogenesis, 86–88
Ketonemia, 89
Ketones, 85
Ketonuria, 89
Kidney disease, 171
  AKI, 171
  CKD, 171, 172
    dietary acid load, reduction of, 176, 177
    metabolic acidosis, 173–175
    NAE, 173
    $NaHCO_3$/sodium citrate, use of, 174, 175
    pattern of acid-base disorders, 173
    treatment, 174
  hemodialysis, 177, 178
  kidney transplantation, 179, 180
  peritoneal dialysis, 179
Kidney transplantation, 179–181
Kidneys, 10, 11
Kyphoscoliosis, 227–229

L
Lactate, 63
Lactic acid, 80, 308
Lactic acidosis, 63, 64
  conditions of
    antiretroviral agents, 70
    linezolid, 70
    MALA, 69, 70
    malignancy, 68, 69
    propofol, 70
    tissue hypoxia, 67, 68
  diagnosis, 71, 72
  dichloroacetate, 74
  D-lactic acidosis, 75
    acute toxicity, 77, 78
    clinical manifestations, 76
    diagnosis, 76
    long-term management, 78
    pathogenesis, 77
    toxicity, 76
    treatment, 77
  due to hereditary/acquired enzyme defects, 71
  hyperlactatemia vs, 65–67
  insulin, 74
  methylene blue, 75
  Na/H exchanger, inhibitors, 75
  $NaHCO_3$ requirements, 72, 73
  production, 64, 65
  renal replacement therapies, 74
  THAM, 73
  thiamine and riboflavin, 74
  treatment, 72
  tribonat, 74
  vasodilators, 75
Laxative abuse, 166, 167, 195, 196
Liddle syndrome, 191, 207
Linezolid, 70
Liver disease, 236, 284
  acid-base balance, 281
    HCO_3^- and NH_4^+ metabolism, 282, 283
    hypoalbuminemia, 283
    ketogenesis, 281
    lactate metabolism, 281
  diarrhea, 287
  high anion gap metabolic acidosis, 285, 286
  metabolic alkalosis, 285
  normal AG metabolic acidosis, 286, 287
  respiratory acidosis, 288
  respiratory alkalosis, 284, 285
  RTA, 287, 288
L-lactate, 63
Low acid load, 182
Lungs, 10

M
Malignancy, lactic acidosis, 68, 69
Malignant hypertension, 192, 203
Mechanical ventilation, 232
Metabolic acidosis, 4, 20, 46, 47, 81, 246, 247, 284, 307
  AG
    high, 42
    low, 43, 44
    normal, 43
  CKD
    adverse effects, 174, 175
    pathophysiology, 173
  critically Ill patients, 263
    clinical manifestations, 267
    L-lactic acidosis, 264–266
    management, 268
  DKA, 88
  drug-induced acid-base disorders, 257–259
  liver disease, 285–287
  mixed acid–base disorders, 244–246
  pregnancy, 300
  TPN, 293, 294
Metabolic alkalosis, 4, 33, 46–48, 185, 199
  acquired causes, 191–194
  causes of, 186, 188
  classification, 188
  clinical manifestations, 196
  course of, 185
  critically Ill patients
    clinical manifestations, 271
    hypercalcemia, 269
    hypertensive emergencies, 270
    hypoalbuminemia, 269, 270
    management, 267, 269–271
    Ringer's lactate, 270
    transfusion, 270
  diagnosis, 196, 197
  differential diagnosis, 203
  drug-induced acid-base disorders, 257, 260
  generation phase, 185
  genetic mechanisms, 190, 191
  GI mechanisms
    congenital chloridorrhea, 195
    laxative abuse, 195, 196
    villous adenoma, 195
    vomiting and nasogastric suction, 194, 195
  liver disease, 285
  maintenance phase, 186, 187
  mixed acid–base disorders, 244–249
  pathophysiology, 188
  pregnancy, 301, 302
  recovery phase, 187
  renal mechanisms, renal transport mechanisms, 188, 189
  respiratory response, 187
  TPN, 294, 296
  treatment, 197–199
Metformin-associated lactic acidosis (MALA), 69, 70
Methanol, 123
Methyl alcohol, 105
  clinical manifestations, 106
  diagnosis, 106
  with dialysis, 107, 108
  without dialysis, 107, 107, 108
  metabolism, 105
  treatment, 106, 107
Methylene blue, 75
Milk-alkali syndrome, 193
Mixed acid–base disorders, 40, 53–55, 243
  analysis of, 244
    metabolic acidosis and metabolic alkalosis, 244–246
    metabolic acidosis and respiratory acidosis, 247
    metabolic acidosis and respiratory alkalosis, 246
    metabolic alkalosis and respiratory acidosis, 248, 249
    metabolic alkalosis and respiratory alkalosis, 247
    triple acid–base disorders, 249
  critically Ill patients, 277, 278
  treatment, 249
    metabolic acidosis and metabolic alkalosis, 250
    metabolic acidosis and respiratory acidosis, 250
    metabolic acidosis and respiratory alkalosis, 250
    metabolic alkalosis and respiratory acidosis, 250
    metabolic alkalosis and respiratory alkalosis, 250
Mixed acid-base disturbances, 284

N
Na/H exchanger, inhibitors, 75
Neomycin, 81
Nephrocalcinosis, 141
Nephrolithiasis, 141
Net acid excretion, 19, 20
Net acid excretion (NAE), 129

CKD, 173
Nitroprusside therapy, 75
Noninvasive positive pressure ventilation (NIPPV), 221, 224
Nonvolatile acids, 8
Normobicarbonatemia, 40
Normocapnia, 40

O
Osmolal gap, 103
Osmotic diarrhea, 162
5-Oxoproline, 117–119

P
Pancreatic fistulas, 165
Pancreatitis, 252–255
Paraldehyde, 120
Parenteral nutrition, 266
pCO_2, 2, 3, 29
Pendred syndrome, 210, 211
Peripheral chemoreceptors, 215
Peritoneal dialysis (PD), 179
pH, 2
  buffers, 9, 10
  kidneys, 10, 11
  lungs, 10
Phosphate
  DKA, 93
Potassium
  DKA, 93
  depletion, 187
Physicochemical method
  acid–base disorders, 28, 29
Physiologic method
  acid–base disorders, 27
pO_2, 1, 3
Polydipsia, 95
Polyuria, 95
Posthypercapnic metabolic alkalosis, 192
Postoperative surgery
  acid-base disorders during, 306, 307
Pregnancy, 299
  metabolic acidosis, 300
  metabolic alkalosis, 301, 302
  respiratory acidosis, 301
  respiratory alkalosis, 299, 300, 302
Preoperative surgery
  acid-base disorders during, 305, 306
Primary acid-base disorders, 4
Primary acid–base disorders, 4
Primary aldosteronism, 191, 209
Primary change, 40
Primary hypercapnia, *See* Respiratory acidosis
Propofol, lactic acidosis, 70
Propylene glycol (PG), 113, 266
  clinical manifestations, 114
  diagnosis, 114
  metabolism, 114
  treatment, 114
Proximal RTA, 179
  autosomal dominant proximal RTA, 135
  autosomal recessive proximal RTA, 134
  carbonic anhydrase deficiency, 135
  causes of, 132, 133
  characteristics of, 133
  clinical manifestations of, 134
  definition, 130
  diagnosis of, 134
  pathophysiology, 131
  renal Fanconi syndrome, 135, 136
  treatment, 137
Proximal tubule, 11, 12
Pyroglutamic acid, 117–119

R
Renal artery stenosis, 192
Renal failure, 266
Renal Fanconi syndrome
  causes of, 135, 136
  definition, 132
  laboratory and clinical manifestations, 133
  pathogenesis, 133
Renal mechanisms, 188, 189
Renal replacement therapies, 74
Renal transport mechanisms, 188, 189
Renal tubular acidosis (RTA), 127, 179
  approach to patient, 147
  distal RTA
    characteristics, 138
    clinical characteristics, 140
    complications, 140, 141
    diagnosis of, 140
    pathophysiology, 138, 139
    treatment, 141, 142
  hyperkalemia, distal RTA with, 142
    causes, 143
    diagnosis, 144, 145
    treatment, 145
  distinguishing features of, 146
  incomplete, 142
  liver disease, 287, 288
  medications, 288
  net acid excretion, 129

Renal tubular acidosis (RTA) (*cont.*)
proximal RTA
autosomal dominant proximal RTA, 135
autosomal recessive proximal RTA, 134
carbonic anhydrase deficiency, 135
causes of, 132, 133
characteristics of, 133
clinical manifestations of, 134
definition, 130
diagnosis of, 134
pathophysiology, 131
renal Fanconi syndrome, 135, 136
treatment, 137
renal Fanconi syndrome
definition, 132
laboratory and clinical manifestations, 133
pathogenesis, 133
types of, 127, 128
urine anion gap, 130
urine osmolal gap, 130
urine pH, 129
Renin-secreting tumor, 204
Renovascular hypertension, 204
Respiratory acidosis, 4, 247, 307
acute respiratory acidosis, 219
acute severe asthma, 220
antibiotics, 221
cardiac manifestations, 219, 221
chronic respiratory acidosis, superimposed on, 220
CNS manifestations, 221
diagnosis, 221, 222
increased CO_2 production, 220
neuromuscular disorders, 220
opiates, 220
renal effects, 221
treatment, 222, 223
chronic respiratory acidosis, 223
clinical manifestations, 224, 225
COPD, 224
diagnosis, 223, 225
OHS, 224
PAHS, 224
treatment, 225, 226
critically Ill patients, 272
causes of, 272
clinical manifestations, 272, 273
management, 273
drug-induced acid-base disorders, 257, 261
liver disease, 288
mixed acid–base disorders, 248, 249
pathophysiology, 216
chest wall and respiratory muscles, abnormalities, 217
CO_2, overproduction of, 216
decreased alveolar ventilation, 216, 217
decreased respiratory center response, 217
impaired gas exchange, 217
secondary physiologic response, 217–219
physiology, 213
CO_2 elimination, 214
CO_2 production, 213
CO_2 transport, 214
ventilation, CNS control of, 214, 215
pregnancy, 301
TPN, 294, 295
Respiratory alkalosis, 4, 201, 246, 305
ABG, 239
acute and chronic respiratory alkalosis, causes of, 233
anxiety-hyperventilation syndrome, 234
CNS diseases, 235
drugs, 235
high altitude, 234, 235
liver disease, 236
pregnancy, 236
pulmonary diseases, 236
sepsis, 236
clinical manifestations
acute respiratory alkalosis, 236, 237
chronic respiratory alkalosis, 237, 238
critically Ill patients, 275, 276
diagnosis, 238
liver disease, 284, 285
mechanism of secondary physiologic response
acute respiratory alkalosis, 233
chronic respiratory alkalosis, 233
mixed acid–base disorders, 247
pathophysiology, 231, 232
pregnancy, 299, 300, 302
secondary physiologic response, 232
serum chemistry, 239
TPN, 295
treatment, 239, 240
Riboflavin, 74
Ringer's lactate, 270
Rubbing alcohol, 114

S
Salicylate intoxication, 115–117
Secondary change, 40
Sepsis, 67, 236
Septic shock, 67
Simple acid–base disorder, 40
Sjögren's syndrome, 153
Small bowl syndrome (SBS), 77
Small intestine, Na^+ and Cl^- transport in, 157–159
Sodium (Na^+), DKA, 92
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, 95
Starvation ketoacidosis, 100
Stool osmolal gap, 163
Strong ion difference (SID), 30, 31
Sulfuric acid, 8
Systemic lupus erythematosus (SLE), 147

T
Thiamine, 74
Tissue hypoxia, 67, 68
Titratable acid, excretion of, 15, 16
Toluene, 119, 120, 149
Toluene ingestion, 142
Topiramate, 152
Total parenteral nutrition (TPN), 293
  metabolic acidosis, 293, 294
  metabolic alkalosis, 294
  respiratory acidosis, 294, 295
  respiratory alkalosis, 295
Total parenteral nutrition-induced hypercapnia, 296
Toxin-induced acid-base disorders, 103, 104
  DEG, 111
    clinical manifestations, 113
    diagnosis, 113
    metabolism, 112
    treatment, 113
  ethylene glycol, 109
    clinical manifestations, 109, 110
    diagnosis, 110, 111
    metabolism, 109
    treatment, 111
  isopropyl alcohol, 114, 115
  methyl alcohol, 105
    clinical manifestations, 106
    diagnosis, 106
    with dialysis, 107, 108
    without dialysis, 107
    hemodialysis, 107, 108
    metabolism, 105
    treatment, 106, 107
  paraldehyde, 120
  propylene glycol, 113
    clinical manifestations, 114
    diagnosis, 114
    metabolism, 114
    treatment, 114
  pyroglutamic acid, 117–119
  salicylate intoxication, 115–117
  toluene, 119, 120
Toxin-induced metabolic acidosis, 266
Transfusion, 270
Tribonat, 74
Trimethoprim-sulfamethoxazole, 81
Triple acid–base disorders, 249
Tris-hydroxymethyl aminomethane (THAM), 73

U
Uncomplicated diarrhea, 169
Urinalysis, 153
Urinary acidification, 19, 20
Urinary-intestinal diversions, 165, 166
Urine anion gap, 130, 148
Urine Cl^-, 203
Urine electrolytes, 205
Urine osmolal gap, 130

V
Vasodilators, 75
Ventilation, CNS control of, 214, 215
Villous adenoma, 165, 195
Volatile acid, 8
Volume deficit, correction of, 91, 92
Volume depletion, 168

W
Water, 161
Weak acids, total concentration, 31